Improving the emergency management of hyperkalaemia

by

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes five original papers and two supplementary papers. With the exception of one paper which is in press (Chapter 2), all other papers have been published in peer reviewed journals.

Date: December 2022

ABSTRACT

Hyperkalaemia is a common electrolyte disorder in hospitalised adult patients and is associated with life-threatening muscle weakness and cardiac arrhythmias if left untreated. The central theme of this project was to improve the emergency management of hyperkalaemia by contributing data to fill important knowledge gaps and shed light on areas of the management where there is still controversy. We investigated the epidemiology, diagnostic aspects, treatment-related adverse effects, the knowledge of medical specialists regarding managing hyperkalaemia and we tested a novel treatment option.

Our retrospective cohort study is the largest African study to report on the frequency, risk factors and outcome of hospitalised adult patients with hyperkalaemia. In-hospital death was high (29%) and acute kidney injury was the strongest predictor of mortality. Fourteen percent of our patients with hyperkalaemia were HIV positive. There was no difference in mortality based on HIV status. Future research should investigate whether the earlier identification and treatment of patients with hyperkalaemia in association with AKI will improve outcomes.

Our scoping review on the adverse effects of insulin therapy for hyperkalaemia is the first comprehensive review of the topic. The prevalence of hypoglycaemia was 17%. Lower insulin doses were associated with a reduced prevalence of severe hypoglycaemia, and continuous infusion of dextrose was associated with a lower overall prevalence. There were no differences in the prevalence of hypoglycaemia by insulin dose, type, rate of administration or timing relative to dextrose. There was also no difference related to dextrose dose. The most important predictor of hypoglycaemia was lower pre-treatment serum glucose concentrations.

In our survey, which tested the knowledge of medical specialists on the emergency management of hyperkalaemia, we found wide variations in their knowledge and practice. Knowledge gaps were identified in all facets of management, particularly around the optimal and safe use of insulin-based therapies. Our findings should be useful in informing the development of consensus-based guidelines and educational materials.

To improve the diagnosis of hyperkalaemia in the emergency department, we performed a method comparison study between point-of-care blood gas analyser (POC-BGA) and laboratory auto-analyser potassium concentrations ($[K^+]$). We found a systematic negative bias of -0.4 mmol/L, with the difference remaining relatively constant across the hyperkalaemic range. We recommend that POC-BGA measurements of $[K^+]$ can therefore

be used, with adjustment for this bias, allowing for rapid diagnosis and the prompt initiation of treatment.

To address the risk of hypoglycaemia after insulin therapy, we investigated a novel treatment for the management of hyperkalaemia. In a randomised, cross-over trial, stable patients on chronic haemodialysis received treatment with either an intravenous dextrose-only bolus or standard insulin-plus-dextrose therapy. In the dextrose-only group, a clinically significant decrease of 0.5 mmol/L in the [K^+] was found, without any episodes of hypoglycaemia. Although the decrease in the [K^+] was greater in the insulin-plus-dextrose group, 20% of the participants developed hypoglycaemia. A dextrose-only bolus is therefore an attractive treatment option especially in busy, resource-limited emergency departments where careful and frequent monitoring of the blood glucose concentration may not be possible.

These studies have highlighted the importance of hyperkalaemia in hospitalised patients and contributed to improvements in the diagnosis and emergency management of this condition. We anticipate that our findings will inform treatment guidelines and inform the training of healthcare workers and students.

ACKNOWLEDGEMENTS

I wish to express my appreciation for all the support which enabled me to complete this project successfully:

I owe a huge debt of gratitude to my supervisors, Professors Razeen Davids and Usuf Chikte, for identifying and harnessing the potential within me. Both were truly instrumental in realising this PhD. Our time spent at Rumi's Café discussing life, and sometimes PhD-related issues, will always be fondly remembered. I am forever indebted to them.

My spark for research was ignited during my time as a senior registrar training in the Division of Nephrology. Before this, I mainly regarded myself as a clinician and built a reputation among undergraduate and postgraduate students as an excellent teacher. During this time, Prof Razeen Davids posed a question asking whether I regard myself as a researcher. My reply was that I was a clinician and teacher, but not a researcher. He responded by saying, "If there were 10 causes for a condition, you would know all of them. However, I would want to identify the 11th cause!" This was a defining moment that sparked my interest in research.

I am grateful to my colleagues in the Division of Nephrology and the Department of Medicine, especially Prof Rafique Moosa and Dr Johan Nel. I am also indebted to all the colleagues who proofread my manuscripts or listened to my presentations and offered many helpful suggestions.

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Hyperkalaemia, defined as a serum potassium concentration ([K^+]) more than or equal to 5.5 mmol/L, is a common electrolyte disorder with the potentially life-threatening consequences of cardiac arrhythmias and muscle weakness. It usually results from reduced renal elimination of potassium and the most important risk factors are therefore kidney disease and drugs which impair the kidney's ability to excrete potassium.

Relevant potassium physiology

Potassium is primarily responsible for maintaining the resting membrane potential (RMP) of cells. This is especially important in the cardiac conduction system and in skeletal muscle. In the presence of hyperkalaemia, the RMP of these cells increases, which predisposes to life-threatening cardiac arrhythmias and respiratory muscle weakness [1-3].

Insulin plays a key role in preventing hyperkalaemia after a dietary potassium load by shifting potassium into liver and muscle cells via a two-step process: (1) activation of the sodium–hydrogen exchanger, NHE-1, allowing sodium (Na^+) entry into cells, followed by (2) activation of the Na^+/K^+–ATPase because of the high intracellular [Na^+]. This pump exports three intracellular Na^+ ions in exchange for two K^+ ions, thereby shifting potassium into cells and contributing to the negative intracellular charge which holds potassium inside cells (Figure 1).

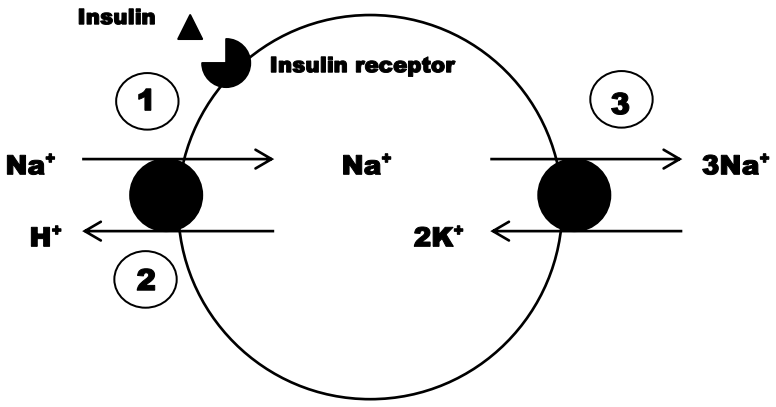


Figure 1. Mechanism of the intracellular potassium shift with insulin. Insulin binds to its receptor (1), which activates the sodium–hydrogen exchanger (2). The intracellular sodium concentration rises, activating the Na^+/K^+–ATPase, which pumps three sodium ions out of the cell in exchange for two potassium ions (3).

While the effect of insulin on blood glucose concentrations (the glycaemic effect) peaks at serum insulin concentrations of ~100 µU/mL, the effect on shifting potassium into cells (the kalaemic effect) occurs at much higher insulin concentrations, around ~500 µU/mL (Figure 2) [4]. This kalaemic response is maintained in patients with diabetes and chronic kidney disease (CKD) [5-7].

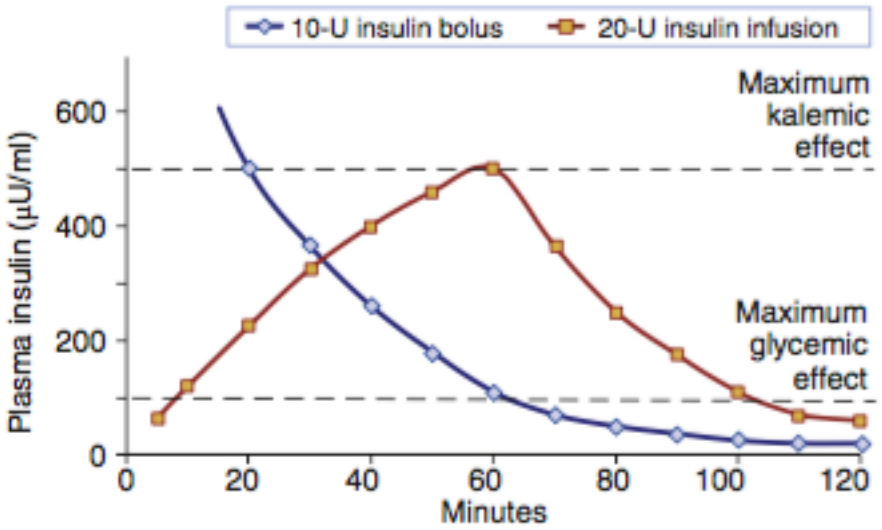


Figure 2. Theoretical comparison of the glycaemic and kalaemic effects of an intravenous insulin bolus (blue) versus a continuous infusion of insulin (red). From Sterns et al. [4].

Epidemiology and risk factors for hyperkalaemia

Variations in the reported incidence and prevalence of hyperkalaemia in hospitalised populations may be due to differences in the definitions of hyperkalaemia as well as differences in the populations studied. The most significant risk factor for the development of hyperkalaemia is kidney disease, an important public health problem

which affects 10–15% of adults worldwide [8, 9]. In developed countries, the main drivers of the CKD epidemic are non-communicable diseases (NCDs) such as diabetes and hypertension [10]. African countries also bear a large and increasing burden of NCDs but, in addition, have high rates of infectious diseases, injuries and pregnancy-related complications which may all contribute to the development of CKD [11]. The causes of CKD, and of hyperkalaemia, are therefore likely to be different in African patients from those patients living in high-income countries. For example, patients with HIV infection may develop hyperkalaemia from acute kidney injury due to diarrhoeal disease or sepsis, from chronic kidney disease due to HIV-associated nephropathy, or from adrenal insufficiency secondary to tuberculosis [12-14]. Trimethoprim, a commonly used drug in HIV patients, can cause hyperkalaemia by inhibiting epithelial sodium channels (ENaC) in the distal nephron [12], causing a reduction in sodium reabsorption and potassium secretion.

Another common risk factor for hyperkalaemia is the use of renin–angiotensin–aldosterone system inhibitors (RAASi). These drugs are often used in patients with CKD for their renoprotective effect, slowing down the progression to end-stage kidney failure (ESKF) [15]. This important benefit comes at the risk of developing hyperkalaemia, which is frequently the reason for stopping RAASi therapy [16, 17]. A large study of CKD patients with and without RAASi therapy reported hyperkalaemia rates of 8.2 and 1.8 per 100 patient-months, respectively, clearly highlighting the additional risk [16]. The use of novel potassium-binding resins such as patiromer [18] and sodium zirconium cyclosilicate [19] have allowed the continuation of RAASi therapy in patients prone to hyperkalaemia, allowing patients to continue to benefit from RAASi treatment. Unfortunately, these resins are not yet available in South Africa, and therefore discontinuation of RAASi is frequently the only alternative for patients that develop hyperkalaemia.

Very few studies on hyperkalaemia have been conducted on the African continent. Furthermore, despite 70% of the world's HIV population living in sub-Saharan Africa, there is a paucity of epidemiological data on hyperkalaemia in this population [20]. A recent systematic review could not identify any studies from Africa reporting on its incidence [21], and only three studies reported on the prevalence of hyperkalaemia [22-24], defined as a [K^+] value of ≥5.5 mmol/L, which was high at 36.7%. More

studies are therefore needed on the frequency, causes and outcomes of hyperkalaemia in patients living in African countries.

The diagnosis of hyperkalaemia in the emergency setting

The symptoms of hyperkalaemia are non-specific and not reliable in the diagnosis of the condition. The identification of typical abnormalities on electrocardiogram (ECG) or the measurement of [K^+] by point-of-care devices allows for rapid diagnosis and the prompt institution of appropriate treatment.

The ECG is a non-invasive investigation which may demonstrate changes which correlate with the severity of the hyperkalaemia. With mild hyperkalaemia ([K^+] 5.5–6.5 mmol/L) peaked, tented T waves in the precordial leads are present. Moderate hyperkalaemia ([K^+] 6.5–7.5 mmol/L) is associated with flattening and disappearance of P waves and varying degrees of atrioventricular blockade. In severe hyperkalaemia ([K^+] >7.5 mmol/L) the QRS complex widens, resulting in fascicular blocks and bundle branch blocks and the appearance of sine waves, which predisposes to ventricular tachycardia, ventricular fibrillation and asystole [25]. The ECG has low sensitivity for identifying hyperkalaemia, however, and patients may suddenly progress from having near-normal ECGs to malignant arrythmias [26-28].

Another method for rapidly identifying hyperkalaemia is by measuring [K^+] using a point-of-care (POC) machine such as a blood gas analyser (POC-BGA). Data on the agreement between POC-BGAs and laboratory auto-analysers are mainly available from retrospective studies. A study in which POC-BGA and laboratory measurements of [K^+] were compared in 50 patients with a cardiac arrest reported mean differences of only 0.1 mmol/L but wide 95% limits of agreement (–1.2 mmol/L to +1.4 mmol/L). Only three patients in this study had a laboratory [K^+] value ≥5.5 mmol/L [29]. A recent retrospective study compared 118 paired samples with [K^+] >6 mmol/L and found that the level of agreement was poor, with a mean difference of 0.62 mmol/L [30]. Prospective studies focusing on patients with hyperkalaemia are needed to confirm these findings.

The emergency treatment of hyperkalaemia

There are four key principles of treatment of hyperkalaemia: (1) stabilisation of the myocardium with calcium salts, (2) shifting serum potassium into cells, (3) enhancing

potassium elimination from the body via the kidney, gut or dialysis, and (4) removal of all sources of potassium intake and stopping drugs which impair potassium excretion.

There are still controversies around many aspects of the management of hyperkalaemia [31]. This PhD focuses mainly on the shifting of potassium into cells using regular (soluble) insulin and dextrose, which is usually recommended as first-line therapy in the emergency management of hyperkalaemia. The optimal way of using insulin therapy to effect maximal potassium shift while avoiding the serious complication of hypoglycaemia is still unclear [4, 32]. Other options for shifting potassium into cells include β2-agonists and sodium bicarbonate. β2-agonists may lower [K^+] to a similar degree to insulin, but around one-third of patients experience a decline of <0.5 mmol/L, and therefore using these agents as monotherapy is not recommended [31]. Sodium bicarbonate is recommended only if associated with a severe degree of acidosis [33].

Hypoglycaemia is a frequent complication of insulin therapy for hyperkalaemia, but this serious adverse effect has not yet been systematically reviewed and is probably under-appreciated. The proportion of patients who develop hypoglycaemia is as high as 75% [32]. Hypoglycaemia may occur up to three hours following insulin treatment and therefore frequent monitoring of the serum glucose concentration is needed to detect this serious complication and prevent it from causing neurological damage.

Many different treatment regimens have been proposed [32], which have variable effects on the reduction of [K^+] and the risk of hypoglycaemia. Insulin can be administered either as an intravenous bolus or as a continuous infusion [32, 34]. Regardless of the regimen, insulin remains the most effective means of reducing serum [K^+] with average reductions of approximately 1.0 mmol/L [32, 34]. One common regimen involves the intravenous bolus administration of 10 units of insulin together with 25 g of dextrose (often as 50 mL of 50% dextrose water). This regimen produces kalaemic concentrations of insulin only transiently. The concentrations remain high enough to lower blood glucose (glycaemic concentrations) for a longer period, increasing the risk of hypoglycaemia [4].

Most of the studies on which the recommended treatment regimens are based have been performed in small groups of patients on chronic haemodialysis [32, 34]. Most

studies used 25 g of dextrose, with rates of hypoglycaemia ranging from 7% to 75% [32]. The risk for hypoglycaemia appears to increase with smaller doses of dextrose and in patients with kidney failure. Poor kidney function increases the half-life of insulin, resulting in hypoglycaemia, which typically occurs 1–3 hours after potassium has been shifted [35, 36]. Insulin types with shorter half-lives, such as lispro and aspart, may reduce the risk of hypoglycaemia in those patients with kidney disease [37]. Patients with diabetes mellitus or higher pre-treatment blood glucose concentrations have a reduced risk of hypoglycaemia [38, 39].

Reducing the risk of hypoglycaemia

Among the recommendations to reduce the risk of hypoglycaemia are using larger amounts of dextrose, administering the dextrose before the insulin bolus, and giving an insulin–dextrose mixture as an infusion over an hour [4, 40, 41]. Another option is to reduce the dose of insulin. Two retrospective studies have reported lower rates of hypoglycaemia when using 5 units as compared to 10 units of insulin, without affecting the efficacy of reducing $[K^+]$ [42, 43].

A novel regimen which combines bolus and continuous infusion of insulin has recently been proposed [4] but has not yet been formally tested. In a 70 kg patient, the regimen involved the bolus administration of 6 units of insulin followed by the continuous infusion of 20 units of insulin together with 60 g of dextrose over an hour [4]. This had the theoretical advantage of rapidly achieving high enough insulin concentrations to shift potassium and maintaining these concentrations over an hour with resultant maximal intracellular shift.

Another attractive alternative is an intravenous dextrose-only bolus. An insulin-free treatment strategy would avoid hypoglycaemia and may shift potassium into cells by eliciting endogenous insulin release in response to the dextrose load. This is of particular importance in busy, resource-limited, emergency departments where the continuous monitoring of blood glucose concentrations may not be adequate because of overstretched and frequently understaffed nursing personnel. There are, however, some theoretical concerns which have been expressed regarding this option: (i) insulin resistance is likely in patients with CKD [5] and (ii) the hyperosmolar dextrose bolus may draw potassium-rich fluid out of cells by solvent drag, paradoxically increasing $[K^+]$ [44-46]. We believed that this treatment option

should be formally tested as insulin resistance in CKD appears to affect only its metabolic actions, not its ability to shift potassium into cells [6], and there are currently no published data to support the concern about solvent drag worsening the hyperkalaemia.

The knowledge and practice patterns of medical staff

There is a paucity of data on the knowledge and practice patterns of doctors regarding the emergency management of hyperkalaemia. A survey that assessed knowledge of the significance, causes and treatment of hyperkalaemia among trainees from a variety of medical and surgical disciplines reported a low overall score of 52% [47]. The lowest scores were achieved for knowledge regarding the normal [K^+] range, the threshold for treating hyperkalaemia and drugs that may result in hyperkalaemia. Another survey of the knowledge of paediatricians regarding the choice and sequence of administration of drugs according to the Advanced Cardiovascular Life Support guidelines during cardiac arrest associated with hyperkalaemia reported that few participants adhered to the guidelines and recommended that a standardised approach be developed to improve management [48]. Lastly, a survey that described the practice patterns of residents and specialist physicians reported wide variations in practice regarding their treatment of hyperkalaemia in patients with and without kidney failure in the emergency department. The authors speculated that this variation may have resulted from concerns regarding the risk of hypoglycaemia when insulin-based therapy was utilised in patients with kidney failure [49].

Central theme and aims of this research project

The central theme of this project was how to improve the emergency management of hyperkalaemia by contributing data to fill important knowledge gaps and shed light on areas of the management where there is still controversy. We anticipate that the findings reported here will lead to improvements in treatment guidelines and inform the training of healthcare workers and students.

Outline of the project

The aims are summarised in Figure 3.

Aim 1: Determine the disease burden in an African setting (Chapter 2)

There is a lack of good epidemiological data on hyperkalaemia from Africa. The few published studies have included convenience samples in patient populations at high risk for the development of hyperkalaemia; large studies of unselected, hospitalised patients are lacking. As a result, in a large, tertiary hospital, we performed a retrospective cohort study of hospitalised adult patients with hyperkalaemia, to establish the incidence and prevalence of hyperkalaemia, the predictors of their [K^+] values and the rates and predictors of in-hospital death. We also investigated the acute management of hyperkalaemia and documented the monitoring of blood glucose concentrations and the rate of hypoglycaemia in patients who received insulin-based therapy. An additional aim was to investigate differences between HIV-positive and -negative patients.

Aim 2: Review adverse effects of treatment (Chapter 3)

Hypoglycaemia is a serious and frequent complication of insulin-based therapy following the management of hyperkalaemia but is often under-appreciated and has not yet been formally studied. We performed a scoping review of hypoglycaemia and other adverse effects related to insulin-based therapy for the treatment of hyperkalaemia to map existing research and identify any knowledge gaps. We followed the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalysis – *Sc*oping *R*eviews (PRISMA-ScR) guidelines. Several bibliographic databases were searched to identify the relevant research, which was imported into Rayyan screening software. The findings are presented as a narrative summary.

Aim 3: Identifying knowledge gaps among medical staff (Chapter 4)

There is a lack of consensus regarding the optimal management of hyperkalaemia, which may result in wide variation in practice and in the guidance provided by medical specialists to junior staff. Using the Research Electronic Data Capture (REDCap) platform, we performed a survey that assessed the knowledge of medical specialists on the emergency management of hyperkalaemia with the focus on insulin-based therapy. The survey tested all aspects of management, including the [K^+] values that would trigger therapy, diagnosis using point-of-care measurements and the ECG, and therapy that included protecting the heart, shifting potassium into

cells, eliminating potassium from the body and stopping drugs that interfere with renal potassium elimination and high potassium-containing foods.

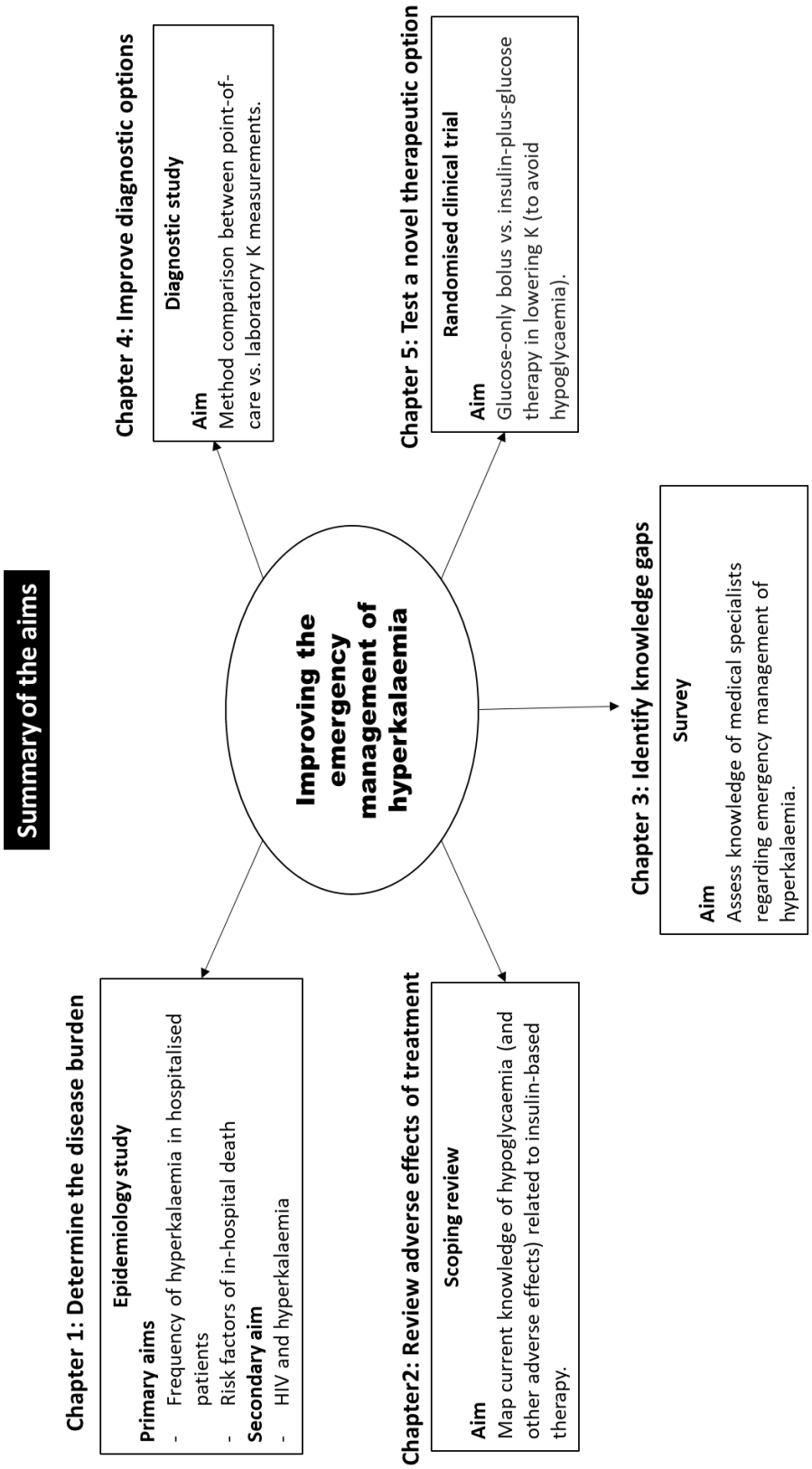
Aim 4: Improving diagnostic options (Chapter 5)

Few studies have reported on the diagnostic accuracy of point-of-care [K^+] relative to laboratory measurements in patients with hyperkalaemia. A reliable point-of-care method of measuring [K^+] in the emergency unit would have a major impact on the rapid diagnosis and prompt treatment of hyperkalaemia and would be likely to improve patient outcomes. We performed a method comparison study of a point-of-care blood gas analyser with a laboratory auto-analyser for the determination of [K^+] during hyperkalaemia in patients with kidney disease. This prospective, cross-sectional study included paired samples from consecutive adult patients with [K^+] ≥ 5.5 mmol/L, who were referred to the nephrology team. Passing–Bablok regression and Bland–Altman analysis were used to compare the two methods.

Aim 5: Testing a novel therapeutic option (Chapter 6)

Our concerns regarding hypoglycaemia and the challenges in monitoring blood glucose concentrations in busy, resource-limited settings led us to consider novel therapeutic options which would avoid this complication altogether. We performed a randomised, crossover clinical trial in patients who were stable on chronic haemodialysis and compared the efficacy of intravenous insulin-plus-glucose therapy to an intravenous glucose-only bolus. The primary outcomes were the magnitude of the fall in the [K^+] values from baseline and the difference in serum [K^+] at 60 minutes between the two groups. The secondary outcomes were related to safety, namely episodes of hypoglycaemia and ECG abnormalities.

Figure 3. Summary of the aims.



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CHAPTER 2

DETERMINE THE DISEASE BURDEN IN AN AFRICAN SETTING

Outcomes of hospitalised patients with hyperkalaemia at a South African tertiary healthcare centre

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Outcomes of hospitalised patients with hyperkalaemia at a South African tertiary healthcare centre

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Summary

Background Hyperkalaemia is a common electrolyte disorder in hospitalised patients. There is a lack of data from Africa on the prevalence, causes and outcomes of patients with hyperkalaemia. We aimed to identify the frequency of hyperkalaemia in hospitalised adults, and to identify any risk factors for in-hospital death.

Methods We conducted a retrospective cohort study of 1921 adult patients admitted to hospital with hyperkalaemia (potassium concentration ([K]) ≥ 5·5 mmol/L) over a one-year period during 2019. Multivariable logistic regression was performed to identify predictors of in-hospital mortality and multilinear regression was used to identify associations with the [K].

Findings We found an incidence rate of 3·7 cases per 100 patient-years. Nearly a third died during hospitalisation. Acute kidney injury (AKI) was common in patients who died (69·2% vs. 41·3%, $P < 0·01$). Age (odds ratio (OR) 1·02, 95% CI 1·01–1·03), [K] (OR 1·38, 95% CI 1·12–1·71), AKI (OR 3·13, 95% CI 2·19–4·47) and acute therapy (OR 1·93, 95% CI 1·40–2·66) were predictors of in-hospital death. AKI ($r = 0·29$, $P < 0·01$) and chronic kidney disease ($r = 0·31$, $P < 0·01$) were associated with the [K]. Fourteen percent of patients with hyperkalaemia were HIV positive with no difference in in-hospital death ($P = 0·75$).

Interpretation This is the largest study reporting on the epidemiology of hyperkalaemia in hospitalised adults from Africa. Hyperkalaemia in association with AKI was a strong predictor of in-hospital death. Late presentation to hospital may be a major factor contributing to poor outcomes.

Funding Self-funded.

Keywords: Incidence; Prevalence; HIV; Potassium; Africa; Mortality

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Introduction

In hospitalised patients, hyperkalaemia is a common electrolyte disorder which may cause life-threatening cardiac arrhythmias if not optimally treated. Variations in the reported incidence and prevalence of hyperkalaemia in hospitalised populations may be due to differences in the definitions of hyperkalaemia as well as in the populations studied. A recent, comprehensive systematic review reported an overall, global prevalence of 8·6% and an incidence of 5·1 cases per 100 person-years for hyperkalaemia, defined as a [K] ≥ 5·5 mmol/L, in hospitalised patients.[1] Few studies were identified from the African continent and none of the studies from Africa reported on the incidence of hyperkalaemia.

CKD, an important public health problem which affects 10–15% of adults worldwide, is the most significant risk factor for the development of hyperkalaemia.[2] In high-income countries (HICs), the main drivers of the CKD epidemic are non-communicable diseases (NCDs) like diabetes and hypertension.[3] African countries also bear a large and increasing burden of NCDs

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Research in context

Evidence before this study

We recently published a systematic review on the incidence and prevalence of hyperkalaemia, and found few studies reporting on the prevalence of hyperkalaemia in hospitalised adult patients from Africa. An overestimated prevalence rate was reported (~36%) and no studies reported on the incidence from Africa.

Only two studies from Africa were identified reporting on the associated mortality of hospitalised patients with hyperkalaemia. These studies included small populations with acute kidney injury only.

We were also interested in the prevalence of hyperkalaemia in the HIV population. High prevalence rates have been reported (20–50%); however, these are overestimations as small, convenience samples of patients were reviewed. Therefore, the true prevalence of hyperkalaemia in hospitalised HIV patients is unknown.

Added value of this study

This is the largest study from Africa to report on the prevalence, and the first to report on the incidence of hyperkalaemia in hospitalised adults. We have also found that fewer patients who died had non-communicable diseases and that acute kidney injury in association with hyperkalaemia was the strongest predictor of death. Late presentation to hospital was speculated to be a factor for poor outcomes.

The proportion of hyperkalaemic patients with HIV was ~14%, lower than what was previously thought. Trimethoprim therapy was more common in HIV patients. There were no differences in in-hospital death between HIV positive and negative patients, although HIV positive patients were mainly female and younger than their HIV negative counterparts.

Implications of all the available evidence

Late presentation to hospital may be a major factor contributing to poor outcomes, regardless of HIV status. Future prospective research should investigate whether earlier identification and treatment of patients with hyperkalaemia associated with AKI will improve outcome.

but, in addition, have high rates of infectious diseases, injuries and pregnancy-related complications which may all contribute to acute and chronic kidney disease. Therefore, the causes of hyperkalaemia are likely to be different in African patients than in patients living in HICs.

Another common risk factor for hyperkalaemia is the use of renin-angiotensin-aldosterone system inhibitors (RAASi). These drugs are often used in patients with CKD as they retard progression to end-stage kidney failure (ESKF) as well as in patients with heart failure, where they improve prognosis.[4] Despite these beneficial effects, drugs in this class are frequently discontinued as a result of hyperkalaemia.[4]

Hyperkalaemia has consistently been reported to be associated with an increased risk of death.[4–6] Few studies regarding the association between hyperkalaemia and mortality have been reported from Africa. A study from Rwanda reported an increased odds of death for hyperkalaemia in patients with AKI-requiring haemodialysis.[7] A study from Ethiopia reported that hyperkalaemia was an independent predictor of in-hospital death in patients admitted to medical wards with AKI.[8]

Although 70% of the world's human immunodeficiency virus (HIV) population lives in sub-Saharan Africa, there is a paucity of epidemiological data on hyperkalaemia in this population.[9] Prevalence rates of 21% to 53% have been reported.[10–13] However, the true prevalence in hospitalised patients is unknown. Apart from NCDs in the HIV population, additional causes of hyperkalaemia are likely to be involved.

Due to the lack of epidemiological data from the African continent, we aimed to identify the frequency of hyperkalaemia in hospitalised adults, and to identify any risk factors for in-hospital death. Comparisons between HIV positive and negative patients were also performed as a secondary outcome.

Methods

We conducted a retrospective, cohort study of all adult patients (18-years-old or more) admitted with or who developed hyperkalaemia (potassium concentration ([K]) of ≥ 5·5 mmol/L) during hospitalisation from 1 January 2019 to 31 December 2019. The study was conducted at Tygerberg Hospital, a 1380-bed tertiary hospital in Cape Town, South Africa, which provides services to approximately 2·5 million people from the Western Cape province. Patients were identified from the database of the National Health Laboratory Service, the national reference laboratory. Exclusion criteria included haemolysed specimens, pseudohyperkalaemia (considered to be present in patients with normal kidney function and normal serum creatine phosphokinase (CPK) concentrations who were not taking drugs that interfere with the renal elimination of K, and who had a platelet count of more than 500×10^9/L or a white cell count of more than 100×10^9/L), patients receiving kidney replacement therapy (chronic dialysis and kidney transplantation), outpatients and patients with diabetic ketoacidosis (DKA). Patients with DKA were excluded since these patients have a total body depletion of K despite hyperkalaemia at presentation and the infusion of insulin is used to treat the DKA rather than the hyperkalaemia. Using a 95% confidence interval, a margin of error of 5%, a population proportion of hospitalised patients with hyperkalaemia of 10%, and a total inpatient population of 52000, the estimated sample size was 138.

Data were extracted from patient electronic records. These included demographic data, and data on comorbid diseases including kidney disease, HIV infection, hypertension, diabetes mellitus and heart disease. Kidney disease was categorised into AKI and CKD. We used the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI[14] and CKD was defined as an estimated glomerular filtration rate (eGFR by the CKD-EPI equation) of less than 60 mL/min/1·73 m² for at least three months. We captured information pertaining to treatment with acute dialysis and the dialysis modalities used. We also reported on the subgroup of dialysed AKI patients admitted to the intensive care unit (ICU). Data were captured on the chronic prescription and use during hospitalisation of angiotensin-converting enzyme inhibitors (ACEi's), angiotensin receptor blockers and spironolactone, trimethoprim (TMP) and non-steroidal anti-inflammatory drugs. Laboratory data included the serum potassium concentration, serum creatinine concentration, CD4 count and serum CPK concentrations. Outcomes data included the length of hospital stay (LOHS) and in-hospital death.

Data captured regarding the acute pharmacological management of the hyperkalaemia included the use of calcium salts, insulin and dextrose doses, beta-2 agonist nebulisations, diuretics, resins such as sodium polystyrene sulphonate, cathartics and dialysis. In addition, we also documented the frequency of capillary blood glucose monitoring following insulin-based therapy and extracted data on adverse events, particularly hypoglycaemia (defined as a glucose concentration of < 4 mmol/L), when insulin-based therapy was used.

The study was conducted in accordance with the Declaration of Helsinki. Permission to conduct the research was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC study number 10988). A waiver of informed consent was granted by HREC due to the retrospective study design.

Role of funding

This study was self-funded. All authors had full access to the data and agreed with the decision to submit for publication.

Statistical analysis

Analyses were performed using Stata version 16·1 (StataCorp LLC, Texas, USA). We used the Shapiro–Wilk test of normality. Numerical data with a normal distribution were described using means and standard deviations while non-normal data were reported as median and interquartile ranges. Histograms, bar charts and box-and-whisker plots were used where appropriate. Chi-squared or Fisher's exact tests were used to compare categorical variables. Student's t-test was used to compare continuous variables and, where the data were not normally distributed, the Mann-Whitney U test was used. Multivariable logistic regression was performed to identify predictors of in-hospital mortality and included the following covariates: [K], age, male sex, HIV positive status, hypertension, diabetes, heart disease, CKD, all KDIGO stages of AKI, acute therapy for hyperkalaemia and RAASi therapy. Multilinear regression was used to identify associations with the [K] and included the following covariates: age, male sex, HIV positive status, hypertension, diabetes, heart disease, CKD, all KDIGO stages of AKI, RAASi therapy and TMP. Pearson correlation matrix and variance inflation factors were used to examine for potential multicollinearity. Kaplan-Meier survival analyses were performed, and associated log-rank tests were determined. We considered a P-value of less than 0·05 to be statistically significant and 95% confidence intervals (CI) were used.

Results

A total of 3183 records were screened. Patients were excluded because of missing data (n = 117), if they were outpatients, including those on chronic dialysis (n = 927), and if they had DKA (n = 34) or pseudohyperkalaemia (n = 184). Therefore, 1921 patients were included in the final analysis. Five hundred and fifty-five patients (28·9%) died during hospitalisation.

During 2019, the total adult admissions were 52243. Thus, the calculated incidence rate of adult patients with hyperkalaemia was 3·7 per 100 patient-years and the period prevalence was 3·7%.

There were no differences in age, sex, HIV-positive status or heart disease between patients who died in hospital and patients discharged alive; however, fewer patients who died had hypertension (45·9% vs. 56.0%, P < 0·01) or diabetes (22·9% vs. 30·0%, P < 0·01). Patients with in-hospital death had more kidney disease (86·6% vs. 67·2%, P < 0·01). AKI was the most common type of kidney disease in both groups but was higher in patients with in-hospital death (69·2% vs. 41·3%, P < 0·01). Compared to those who survived, more patients who died presented with KDIGO stage 3 AKI (56·8% vs. 41·4%, P < 0·01). Mortality was higher for dialysed AKI patients admitted to the ICU as compared to patients managed in the general wards (72·0% vs. 28·8%, P < 0·01). More patients who were discharged alive were prescribed RAASi therapy as chronic medication prior to hospitalisation as well as during hospitalisation (31·2% vs. 42·9%, P < 0·01) of which ACEi's were the most common (27·6% vs. 38·3%, P < 0·01) (Table 1).

The median [K] was higher in patients who died during hospitalisation (6·0 [IQR 5·7–6·6] mmol/L vs. 5·8 [IQR 5·6–6·1] mmol/L, P < 0·01). Patients who died during hospitalisation also had a higher proportion of patients with [K]'s of 6 mmol/L or more. Although less

Demographic data	In-hospital death		*P*-value
	Yes *n*% = 555 (28·9)	No *n*% = 1366 (71·1)	
Age, median (IQR)	55 (39–67)	54 (37–66)	0·22
Male, n%	315 (56·8)	744 (54·5)	0·36
Comorbidities, n%			
HIV, n%	78 (14·1)	187 (13·7)	0·75
Hypertension, n%	255 (45·9)	765 (56·0)	<0·01
Diabetes mellitus, n%	127 (22·9)	410 (30·0)	<0·01
Heart disease, n%	79 (14·2)	189 (13·8)	0·86
Kidney disease, n%	482 (86·8)	918 (67·2)	<0·01
AKI, n%	384 (69·2)	564 (41·3)	<0·01
Stage 1	90 (23·4)	213 (37·8)	<0·01
Stage 2	76 (19·8)	117 (20·8)	
Stage 3	218 (56·8)	233 (41·4)	
Number of AKI patients dialysed, n%	33 (2·4)	44 (3·2)	0·08
Dialysis modality for AKI patients, n%			
Intermittent haemodialysis	27 (81·8)	41 (93·2)	0·26
Slow low efficiency daily dialysis	6 (18·2)	3 (6·8)	
Type of ward for dialysed AKI patients:			
General ward	15 (2·7)	37 (2·7)	<0·01
ICU	18 (3·2)	7 (0·5)	
Dialysis modality for AKI patients in the ICU, n%			
Intermittent haemodialysis	16 (88·9)	5 (71·4)	0.13
Slow low efficiency daily dialysis	2 (11·1)	2 (28·6)	
Chronic kidney disease, n%	96 (17·3)	352 (25·8)	<0·01
Drugs associated with hyperkalaemia, n%			
Any RAASi	173 (31·2)	586 (42·9)	<0·01
ACEi	153 (27·6)	523 (38·3)	<0·01
ARB	26 (4·7)	62 (4·5)	0·89
Spironolactone	32 (5·8)	119 (8·7)	0·03
TMP	13 (2·3)	48 (3·5)	0·18
NSAIDs	22 (4·0)	67 (4·9)	0·37
Other drugs, n%			
ART	43 (7·7)	112 (8·2)	0·74
Loop diuretics	148 (26·7)	389 (28·5)	0·40
Thiazide diuretics	68 (12·3)	228 (16·7)	0·02
Clinical and laboratory data			
[K] (mmol/L), median (IQR)	6·0 (5·7–6·6)	5·8 (5·6–6·1)	<0·01
[K] categories, n%			
5·5–5·9 mmol/L	243 (43·8)	892 (65·3)	<0·01
6·0–6·9 mmol/L	220 (39·6)	370 (27·1)	
≥7·0 mmol/L	92 (16·6)	104 (7·6)	
Overall creatinine (µmol/L), median (IQR)	242 (125–520)	137 (83–29)	<0·01
eGFR (CKD) (mL/min/1·73m^2), median (IQR)	8·7 (4·2–22·4)	19·4 (6·9–36·2)	<0·01
Creatinine (AKI) (µmol/L), median (IQR)	268 (147–526)	185 (124–409)	<0·01
CD4 count (cells/mm^3), median (IQR)	140 (60–340)	189 (79–376)	0·23
CPK (IU/L), median (IQR)	2958 (518–7869)	2171 (450–7718)	0·73
LOHS (days), median (IQR)	2 (0–7)	8 (3–16)	<0·01

***Table 1*: Comparison of baseline characteristics of hyperkalaemic patients with in-hospital death vs. those discharged alive.**
Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; AKI, acute kidney injury; ICU, intensive care unit; RAASi, renin-angiotensin-aldosterone system inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TMP, trimethoprim; NSAIDs, non-steroidal anti-inflammatory drugs; ART, antiretroviral therapy; [K], potassium concentration; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; CPK, creatine phosphokinase; LOHS, length of hospital stay.

patients with in-hospital death had CKD, their median eGFR was lower (8·7 [IQR 4·2–22·4] mL/min/1·73 m^2 vs. 19·4 [IQR 6·9–36·2] mL/min/1·73 m^2, P < 0·01). Also, median serum creatinine concentrations at presentation were higher in patients with AKI who died during hospitalisation (268 [IQR 147–526] µmol/L vs. 185 [IQR 124–409] µmol/L, P < 0·01). In-hospital death occurred soon after the diagnosis of hyperkalaemia (2 [IQR 0–7] days) (Table 1).

More patients who died during hospitalisation received acute therapies (37·5% vs. 18·2%, P < 0·01). However, there were no differences between groups regarding those treated with insulin and dextrose therapy, salbutamol nebulisation, intravenous sodium bicarbonate, sodium polystyrene sulfonate and acute dialysis. More patients with in-hospital death had capillary blood glucose monitoring (38·6% vs. 23·7%, P < 0·01) and had more documented hypoglycaemic events (13·1% vs. 4·0%, P < 0·01) (Table 2).

In-hospital death was associated with age (odds ratio (OR) 1·02, 95% CI 1·01–1·03), [K] (OR 1·38, 95% CI 1·12 –1·71), hypertension (OR 0·62, 95% CI 0·42–0·92), AKI (OR 3·13, 95% CI 2·19–4·47), acute therapy (OR 1·93, 95% CI 1·40–2·66) and RAASi therapy (OR 0·66, 95% CI 0·45–0·95) were all predictors of in-hospital death on multivariable logistic regression (Figure 1). Only AKI (r=0·29, 95% CI 0·20-0·38, P < 0·01) and CKD (r = 0·31, 95% CI 0·20-0·42, P < 0·01) were associated with the [K] on multilinear regression (Table 3).

Figure 2 shows a regression analysis of the relationship between in-hospital death and the [K] after adjustment for age, sex, HIV positive status, hypertension, diabetes, heart disease, kidney disease, RAASi and TMP therapy. There was a progressive increase in the death rate within 24 hours of the hyperkalaemia diagnosis as the [K] range increased (Figure 3). AKI (Figure 4A), patients not prescribed RAASi therapy (Figure 4B), and acute therapy (Figure 4C) were associated with in-hospital death on Kaplan-Meier survival analysis; however, sex (log-rank P = 0·92), HIV positive status (log-rank P = 0·70), CKD (log-rank P = 0·72) and heart disease (log-rank P = 0·87) were not associated.

Regarding our secondary outcome, 13·8% (n = 265) of patients with hyperkalaemia were HIV positive. These patients were younger (39 [IQR 32-48] years vs. 55 [IQR 39–65] years, P < 0·01), mostly female (54·3% vs. 42·9%, P < 0·01), and had fewer NCDs (Table 4). Less HIV positive patients were using RAASi therapy (17% vs. 43·3%, P < 0·01); however, more received treatment with TMP (15·8% vs. 1·3%, P < 0·01). Regarding laboratory data, there were no differences between HIV positive and negative patients in [K], serum creatinine concentration at presentation or eGFR in CKD patients; however, the median creatinine concentration for patients with AKI was higher in the HIV positive group (368 [IQR 172-843] µmol/L vs. 225 [IQR 130-499] µmol/L, P < 0·01). There was no difference in in-hospital death between HIV positive and negative patients (29·4% vs. 28·4%, respectively, P = 0·75).

Acute therapies	In-hospital death		*P*-value
	Yes	No	
Received acute therapy by in-hospital death, n%	208 (37·5)	249 (18·2)	<0·01
[K] category, n%			
5·5–5·9 mmol/L	53 (25·5)	71 (28·5)	0·70
6·0–6·9 mmol/L	98 (47·1)	111 (44·6)	
≥7 mmol/L	58 (27·9)	67 (26·9)	
Calcium gluconate therapy, n%	181 (87·0)	216 (86·7)	0·98
Insulin therapy, n%	176 (84·6)	224 (90·0)	0·06
Insulin dose, n%			
≥10 units, n%	170 (96·6)	216 (96·4)	0·52
<10 units, n%	8 (4·5)	8 (3·6)	0·47
No. of insulin shifts, median (IQR)	1 (1–1)	1 (1–1)	
50% dextrose, n%	183 (88·0)	229 (91·9)	0·09
50% dextrose volume, n%			
20 mL	3 (1·6)	7 (3·1)	0·84
50 mL	148 (80·9)	185 (80·8)	
100 mL	28 (15·3)	35 (15·3)	
200 mL	0 (0)	1 (0·4)	
Other*	1 (0·5)	1 (0·4)	
Salbutamol, n%	35 (16·8)	30 (12·0)	0·15
Sodium bicarbonate, n%	30 (14·4)	25 (10·0)	0·15
Sodium polystyrene sulfonate, n%	35 (16·8)	52 (20·9)	0·27
Other cathartics, n%	16 (7·7)	35 (14·1)	0·03
Acute dialysis, n%	27 (13·0)	28 (11·2)	0·57
Capillary glucose monitoring, n%	68 (38·6)	53 (23·7)	<0·01
Hypoglycaemic events, n%	23 (13·1)	9 (4·0)	<0·01

***Table 2*: Acute therapies for hyperkalaemic patients with in-hospital death vs. those discharged alive.**
Abbreviations: [K], potassium concentration; IQR, interquartile range. *Other: 200 mL 5% dextrose.

Discussion

This is the largest study to report on the frequency, risk factors, acute management, and mortality of hospitalised adult patients with hyperkalaemia from the African continent. We found a lower frequency of hyperkalaemia in hospitalised patients. A recent systematic review reported a prevalence of 8·6% and an incidence rate of 5·1 cases per 100 person-years for hospitalised patients when hyperkalaemia was defined as a [K] of more than or equal to 5·5 mmol/L.[1] However, these frequencies included patients receiving kidney replacement therapy. No studies from the African continent reported on incidence, and only three reported on the prevalence of hyperkalaemia,[13,15,16] ([K] ≥ 5·5 mmol/L), which was high at 36·7%. This is an overestimate since these studies were small and were convenience samples of patients at high risk for the development of

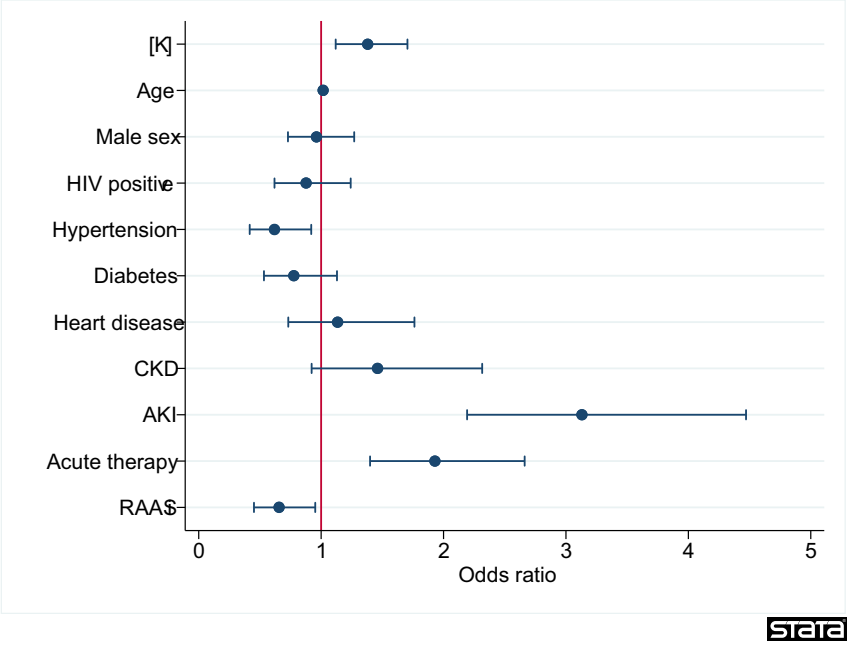

Figure 1. Multivariable logistic regression analysis for predictors of in-hospital death.
Abbreviations: [K], potassium concentration; HIV, human immunodeficiency virus; CKD, chronic kidney disease; AKI, acute kidney injury; RAASi, renin-angiotensin aldosterone system inhibitor.

hyperkalaemia, such as patients with CKD, AKI, or a high burden of infectious disease. Our lower prevalence and incidence rates were probably the result of the inclusion all adult hospitalised patients, and the exclusion of patients with pseudohyperkalaemia, patients receiving kidney replacement therapy and patients with DKA.

We found high in-hospital mortality of 29%. Another study reported a similar mortality rate of 30%.[17] A large meta-analysis reported that the risk of all-cause mortality was increased by 22% when hyperkalaemia was defined as a [K] of more than 5·5 mmol/L.[18] Recently, researchers using a propensity-matched cohort reported 29% higher odds of short-term all-cause mortality following a single episode of hyperkalaemia. We also found a progressive increase in mortality rate within the first 24 hours of the hyperkalaemia diagnosis with rising [K] ranges (Figure 3). This was similar to another study in patients with CKD.[4] Interestingly, patients without CKD had a higher risk of death across all [K] ranges as compared to patients with stage 5 CKD. We speculate that our high mortality may be related to late presentation since kidney function was more severe in patients who died. Factors that may contribute to this

Potassium concentration (mmol/L)	Coefficient	Standard error	t	*P*-value	95% CI
Age (years)	-0·001	0·001	-0·91	0·37	-0·004 to 0·001
Male sex	0·01	0·04	0·18	0·86	-0·07 to 0·08
HIV positive	-0·02	0·05	-0·35	0·73	-0·12 to 0·08
Hypertension	-0·02	0·06	-0·37	0·71	-0·13 to 0·09
Diabetes	0·02	0·05	0·36	0·72	-0·08 to 0·12
Heart disease	-0·08	0·06	-1·34	0·18	-0·20 to 0·04
CKD	0·31	0·06	5·61	<0·01	0·20 to 0·42
AKI	0·29	0·04	6·59	<0·01	0·20 to 0·38
Any RAASi	-0·07	0·05	-1·37	0·17	-0·17 to 0·03
Trimethoprim	-0·04	0·09	-0·42	0·67	-0·22 to 0·14

***Table 3*: Multilinear regression for predictors of the potassium concentration.**
Abbreviations: HIV, human immunodeficiency virus; RAASi, renin-angiotensin-aldosterone system inhibitor; CKD, chronic kidney disease; AKI, acute kidney injury.

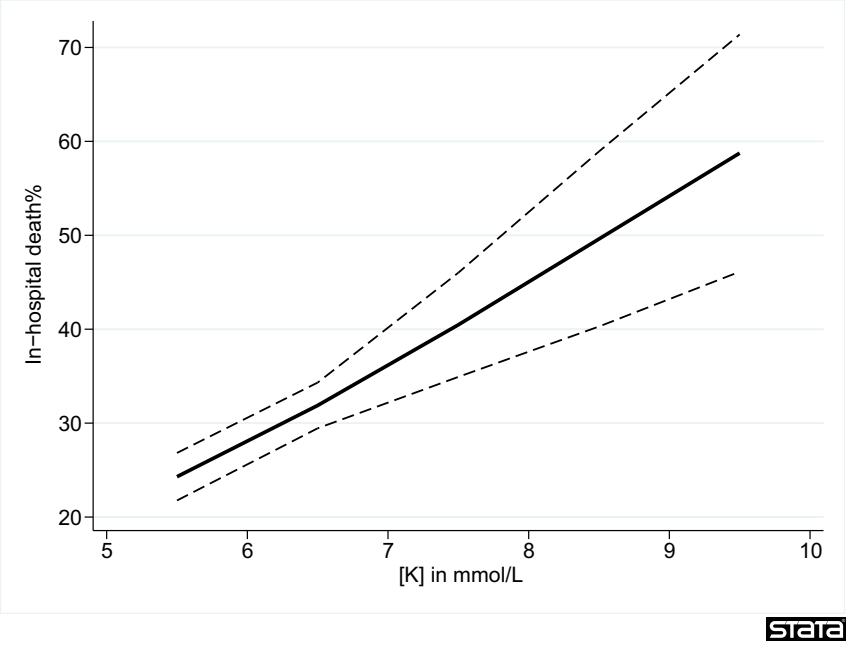

Figure 2. Regression plot of the association between in-hospital death and [K] after adjustment for age, sex, HIV, hypertension, diabetes, heart and kidney disease, RAASi and trimethoprim therapy.

Solid black line represents the mean in-hospital death. Dashed lines represent 95% confidence intervals. Abbreviation: [K], potassium concentration.

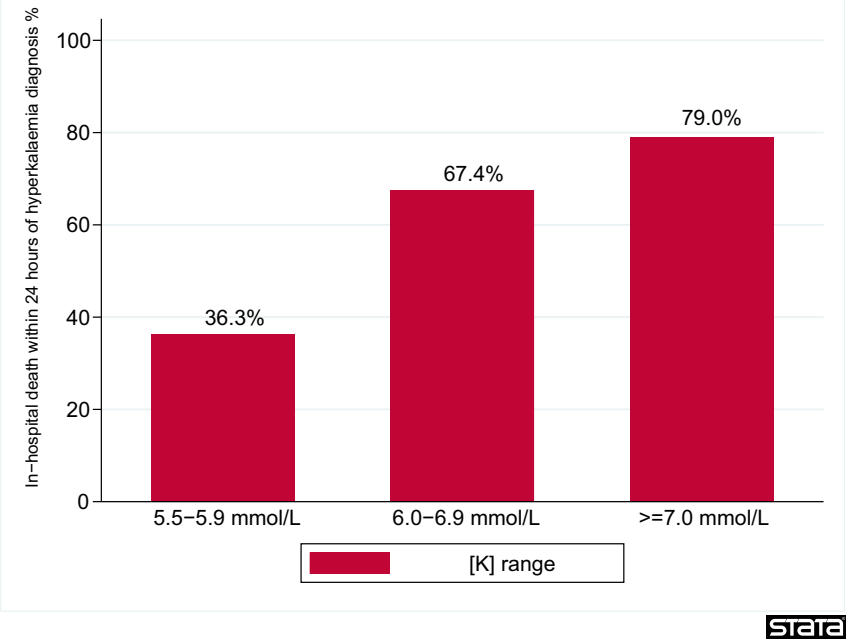

Figure 3. Death rate within 24 hours of hyperkalaemia diagnosis.

Abbreviations: [K], potassium concentration. [K] 5.5-5.9 mmol/L, $n = 243$; [K] 6.0-6.9 mmol/L, $n = 220$, [K] ≥ 7 mmol/L, $n = 92$.

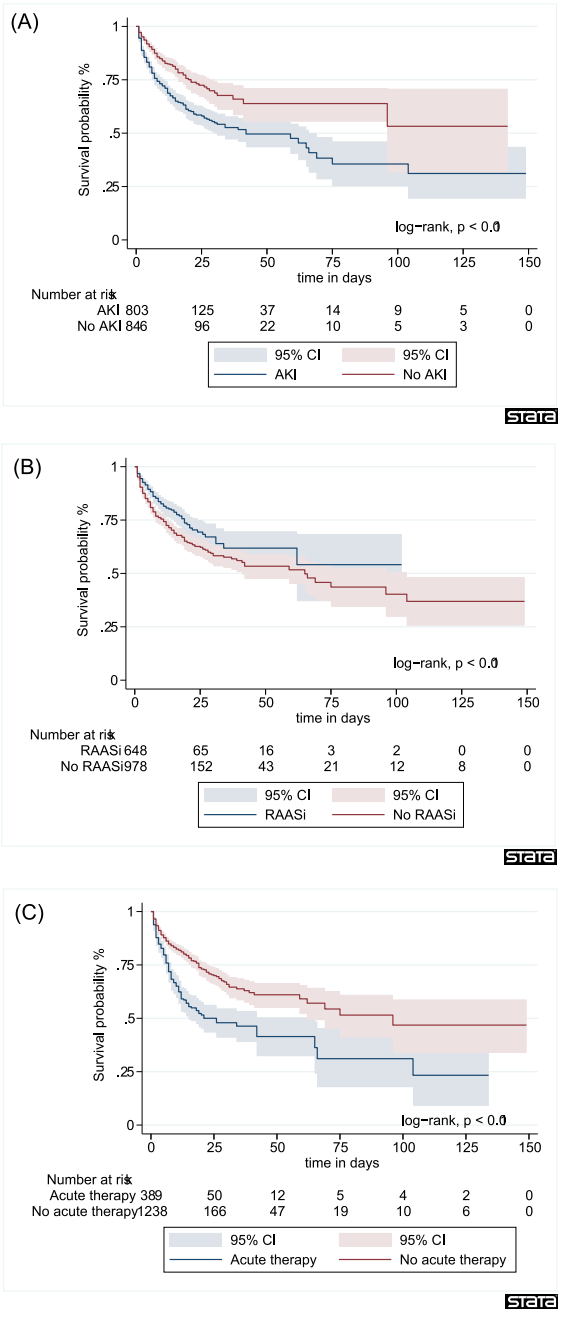

Figure 4. Kaplan-Meier survival analysis for the association between AKI (A), RAASi therapy (B) and acute therapy (C) and in-hospital death.

Abbreviations: AKI, acute kidney injury; RAASi, renin-angiotensin aldosterone system inhibitors; CI, confidence intervals.

include accessibility, affordability, and availability of health services on account of rural domicile, poor access to transport and seeking initial healthcare from traditional healers.

Kidney disease was more common in patients who died and was mainly related to AKI. AKI was also the strongest predictor of death on regression analysis and was associated with severity of the hyperkalaemia. In addition, AKI was more severe at the time of presentation in patients who died. This may be related to late presentation. With public sector acute dialysis services in the province centralised to only two major centres, healthcare workers at peripheral hospitals may delay referral until dialysis initiation is imminent. At our centre, dialysis is initiated at the discretion of the treating nephrologist. As a result of resource constraints, traditional indications for dialysis initiation are used. A randomized trial reported higher 60-day mortality in AKI patients when a more delayed strategy to dialysis initiation was used.[19] Oliguria for more than three days and serum urea concentrations greater than 40 mmol/L were predictors of death. Since more patients who died had KDIGO stage 3 AKI at the time of admission, late presentation rather than lack of dialysis services is a major factor for delayed dialysis initiation at our centre.

We have previously reported high in-hospital mortality rates for patients with AKI that was predominantly caused by infectious disease, trauma and pregnancy-related complications.[20,21] Regardless of the cause, the abrupt loss of kidney function may be associated with a rapid rate of rise in the [K], which has been identified as a factor predisposing to cardiac arrhythmias and death.[22,23]

RAASi therapy use was less common among patients who died. An explanation for this may have been higher [K]s, which is frequently a rate-limiting factor for its use. However, since fewer were hypertensive, diabetic or had CKD, the prescription of RAASi therapy was less frequent. Therefore, despite continued RAASi therapy use in the face of hyperkalaemia, a mortality benefit was observed. This may highlight the importance of continuing RAASi therapy. A recent meta-analysis reported lower all-cause mortality and recurrent adverse kidney outcomes despite continued exposure to RAASi therapy after the onset of AKI.[24] However, the risk of hyperkalaemia was higher when RAASi therapy was continued. Another study that investigated the association of RAASi therapy and all-cause mortality in patients with CKD reported a survival benefit in patients that continued RAASi therapy compared to those where therapy was discontinued.[25] Hyperkalaemia was a common reason for its discontinuation. The decision to discontinue RAASi therapy may depend on several factors such as the rate at which hyperkalaemia evolves, the severity of hyperkalaemia, and associated comorbidities. We did not document the proportion of patients in which RAASi therapy was discontinued during hospitalisation. Novel potassium-binding resins, such as patiromer and sodium zirconium cyclosilicate, have allowed patients prone to hyperkalaemia to benefit from the continued use of RAASi-therapy.[26,27] We do not have access to these novel resins. We speculate that access to these resins may have resulted in a lower

	HIV positive *n*% = 265 (13·8)	HIV negative *n*% = 964 (50·2)	*P*-value
Demographic data			
Age, median (IQR)	39 (32–48)	55 (38·5–64·5)	<0·01
Male, n%	121 (45·7)	550 (57·1)	<0·01
Comorbidities, n%			
Hypertension	6 (2·3)	549 (57·0)	<0·01
Diabetes mellitus	27 (10·2)	291 (30·2)	<0·01
Heart disease	16 (6·0)	136 (14·1)	<0·01
Kidney disease	180 (67·9)	701 (72·7)	0·11
AKI	135 (50·9)	468 (48·5)	0·48
CKD	44 (16·6)	232 (24·1)	0·01
Drugs associated with hyperkalaemia, n%			
Any RAASi	45 (17·0)	418 (43·3)	<0·01
ACEi	42 (15·8)	382 (39·6)	<0·01
ARB	2 (0·7)	43 (4·5)	<0·01
Spironolactone	7 (2·6)	85 (8·8)	<0·01
TMP	42 (15·8)	13 (1·3)	<0·01
NSAIDs	9 (3·4)	66 (6·8)	0·04
Other drugs, n%			
ARVs	152 (57·4)	N/A	–
Loop diuretics	39 (14·7)	302 (31·3)	<0·01
Thiazide diuretics	25 (9·4)	161 (16·7)	<0·01
Clinical and laboratory data			
[K] (mmol/L), median (IQR)	5·8 (5·6–6·2)	5·8 (5·6–6·3)	0·81
[K] categories, n%			
5·5–5·9 mmol/L	158 (59·6)	577 (60·0)	0·89
6·0–6·9 mmol/L	81 (30·6)	284 (29·5)	
≥7·0 mmol/L	26 (9·8)	103 (10·7)	
Overall creatinine (µmol/L), median (IQR)	174 (79–572)	157 (91–414)	0·38
eGFR (CKD) (mL/min/1·73m^2), median (IQR)	9·8 (3·7–31·3)	15·3 (5·2–33·5)	0·30
Creatinine (AKI) (µmol/L), median (IQR)	368 (172–843)	225 (130–499)	<0·01
CD4 count (cells/mm^3), median (IQR)	181 (73–366)	N/A	–
LOHS from first hyperkalaemia (days), median (IQR)	6 (2–14)	7 (2–14)	0·82
In-hospital outcome			
Died	78 (29·4)	274 (28·4)	0·75

***Table 4*: Comparison of baseline characteristics of hyperkalaemic patients with in-hospital death vs. those discharged alive by HIV status.**
Abbreviations: IQR, interquartile range; HIV, human immunodeficiency virus; RAASi, renin-angiotensin-aldosterone system inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TMP, trimethoprim; NSAIDs, non-steroidal anti-inflammatory drugs; ART, antiretroviral therapy; [K], potassium concentration; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; CPK, creatine phosphokinase; LOHS, length of hospital stay.

mortality rate for patients in whom RAASi therapy may have been discontinued due to hyperkalaemia.

More patients who died received acute therapy despite no differences in [K]. Other factors, such as greater illness severity and more frequent electrocardiographic changes, or arrhythmias may have resulted in poorer outcomes. Another finding of concern was the infrequent blood glucose monitoring along with the low number of documented episodes of hypoglycaemia. Hypoglycaemia may occur up to six hours following insulin-based therapy. The infrequent capillary blood glucose monitoring was not surprising as a recent survey reported that only 22% of medical specialists monitor the blood glucose beyond two hours following insulin-based therapy.[28] A systematic review found that hypoglycaemia may occur in as many as 18% of patients receiving insulin-based therapy for the treatment of hyperkalaemia and up to 30% when 25 g of dextrose is used.[29] Since 90% of our cohort received treatment with 25 g dextrose, episodes of hypoglycaemia may have been missed.

Regarding the secondary outcome, approximately 14% of patients with hyperkalaemia were HIV positive. This proportion mirrors the national population prevalence of HIV infection of 13·1%.[30] However, this proportion may be an underestimate since the HIV status was unknown in more than a third of our cohort. HIV-infected patients who died were younger,

predominantly female and had fewer NCDs. They were less likely to be prescribed RAASi therapy; however, more were using TMP, several of them being treated for *Pneumocystis jiroveci* pneumonia. Other diagnoses in the HIV-positive group included cervix carcinoma, lymphoma, Kaposi's sarcoma and disseminated tuberculosis. There were no differences in mortality between HIV-positive and negative patients. Despite South Africa having the largest antiretroviral therapy (ART) programme in the world, patients continue to be diagnosed late as evidenced by the AIDS-defining diagnoses, low CD4 counts and the low proportion of patients using ART at admission. Again, the most common comorbidity in HIV patients associated with hyperkalaemia was AKI. Although there was no difference in the proportion of patients with AKI between the groups, the severity was greater in HIV patients, which might be related to late presentation.[20]

This is the largest study from the African continent to report on the frequency, risk factors, acute management, and mortality of hospitalised adult patients with hyperkalaemia. It is also the largest study describing the frequency, risk factors and outcomes of hyperkalaemia in patients with HIV infection. The exclusion of patients with pseudohyperkalaemia improved the accuracy of our findings. There were also some limitations. As a result of the retrospective design, there were missing data; however, data was considered to be missing completely at random since we were dependent on documents being scanned and placed onto the electronic platform. Since we used electronic data records, the quality of the available data varied. As a result of poor documentation, the underlying illness associated with AKI, which may have explained the strong association of AKI with in-hospital death, was not captured. We did not capture the prescription of beta-blocker therapy which may contribute to hyperkalaemia. Also, since this was a single-centre study, our findings may not be extrapolated beyond our clinical context.

In summary, this is the largest study reporting on the epidemiology of hyperkalaemia in hospitalised adult patients from Africa. Our in-hospital mortality was high. Hyperkalaemia in association with AKI was a strong predictor of in-hospital death. The prevalence of HIV was high but was similar to the national HIV prevalence. Late presentation to hospital may be a major factor contributing to poor outcomes, regardless of HIV status. Future prospective research should investigate whether earlier identification and treatment of patients with hyperkalaemia associated with AKI will improve outcome.

Contributors

MY Chothia: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualisation, writing – original draft, and writing – review & editing. UMEC and MRD: conceptualisation, methodology, supervision, validation, writing – review & editing. AEZ: resources, validation, writing – review & editing. DM, NF, AW, EvV and TD: investigation, validation, writing – review & editing.

Data sharing statement

Deidentified individual participant data will be made available on request to the corresponding author, after fulfilling legal and regulatory requirements and with permission from the Health Research Ethics Committee of Stellenbosch University.

Declaration of interests

The authors declare that they have no competing interests.

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CHAPTER 3

REVIEW ADVERSE EFFECTS OF TREATMENT

Hypoglycaemia due to insulin therapy for the management of hyperkalaemia in hospitalised adults: a scoping review

Published paper:

Chothia MY, Humphrey TH, Schoonees A, Chikte UME, Davids MR. Hypoglycaemia due to insulin therapy for the management of hyperkalaemia in hospitalised adults: a scoping review. PLOS ONE 2022. 17(5): e0268395

PLOS ONE

RESEARCH ARTICLE

Hypoglycaemia due to insulin therapy for the management of hyperkalaemia in hospitalised adults: A scoping review

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Abstract

Introduction

Hyperkalaemia is a very common electrolyte disorder encountered in hospitalised patients. Although hypoglycaemia is a frequent complication of insulin therapy, it is often under-appreciated. We conducted a scoping review of this important complication, and of other adverse effects, of the treatment of hyperkalaemia in hospitalised adults to map existing research on this topic and to identify any knowledge gaps.

Materials and methods

We followed the PRISMA-ScR guidelines. Studies were eligible for inclusion if they reported on any adverse effects in hospitalised patients ≥18-years-old, with hyperkalaemia receiving treatment that included insulin. All eligible research from 1980 to 12 October 2021 were included. We searched Medline (PubMed), Embase (Ovid), the Cochrane Library, CINHAL, Africa-Wide Information, Web of Science Core Collection, LILACS and Epistemonikos. The protocol was prospectively registered with the Open Science Framework (https://osf.io/x8cs9).

Results

Sixty-two articles were included. The prevalence of hypoglycaemia by any definition was 17.2% (95% CI 16.6–17.8%). The median timing of hypoglycaemia was 124 minutes after insulin administration (IQR 102–168 minutes). There were no differences in the prevalence of hypoglycaemia when comparing insulin dose (<10 units vs. ≥10 units), rate of insulin administration (continuous vs. bolus), type of insulin (regular vs. short-acting) or timing of insulin administration relative to dextrose. However, lower insulin doses were associated with a reduced prevalence of severe hypoglycaemia (3.5% vs. 5.9%, P = 0.02). There was

no difference regarding prevalence of hypoglycaemia by dextrose dose (≤25 g vs. >25 g); however, prevalence was lower when dextrose was administered as a continuous infusion compared with bolus administration (3.3% vs. 19.5%, P = 0.02). The most common predictor of hypoglycaemia was the pre-treatment serum glucose concentration (n = 13 studies), which ranged from < 5.6–7.8 mmol/L.

Conclusion

This is the first comprehensive review of the adverse effects following insulin therapy for hyperkalaemia. Hypoglycaemia remains a common adverse effect in hospitalised adults. Future randomised trials should focus on identifying the optimal regimen of insulin therapy to mitigate the risk of hypoglycaemia.

Introduction

Hyperkalaemia is a very common electrolyte disorder encountered in hospitalized patients [1] and, if left untreated, may result in life-threatening cardiac arrhythmias and death. The emergency treatment of hyperkalaemia includes shifting potassium into cells using intravenous insulin, with dextrose added before, with or after insulin administration to prevent hypoglycaemia.

Hypoglycaemia is a frequent complication of insulin therapy, but this serious adverse effect has not yet been systematically studied and is probably under-appreciated by most clinicians. In published reports, the proportion of patients who develop hypoglycaemia is as high as 75% [2]. Hypoglycaemia has been reported to occur up to six hours following insulin treatment and therefore frequent monitoring of the serum glucose concentration is needed to detect this serious complication and prevent it from causing neurological damage [3].

Many different treatment regimens have been proposed, which have variable effects on the serum potassium concentration (K^+) and the risk of hypoglycaemia. Insulin can either be administered as an intravenous bolus or as a continuous infusion [2, 4]. Regardless of the regimen, insulin remains the most effective non-dialytic method for reducing serum K^+, with average reductions of approximately 1.0 mmol/L at one hour [2, 4]. One common regimen involves the intravenous bolus administration of 10 units of insulin together with 25 g of dextrose (often as 50 ml of 50% dextrose water). The insulin concentrations needed to shift potassium into cells remain above the threshold concentration only transiently; however, it remains high enough to lower blood glucose (glycaemic concentrations) for a longer period, increasing the risk of hypoglycaemia [5].

Most of the studies on which the recommended treatment regimens are based have been performed in small groups of patients with kidney failure who are being treated with chronic haemodialysis [2, 4]. Most studies used 25 g of dextrose, with the prevalence of hypoglycaemia ranging from 7% to 75% [2]. The risk for hypoglycaemia appears to increase when using smaller doses of dextrose and in patients with kidney failure. Poor kidney function increases the half-life of insulin, resulting in hypoglycaemia which typically occurs 1–3 hours after insulin administration [6, 7]. Insulins with shorter half-lives, such as lispro and aspart, may reduce the risk of hypoglycaemia in those patients with kidney disease [8]. Patients with diabetes mellitus or higher pre-treatment blood glucose concentrations have a reduced risk of hypoglycaemia [9, 10].

Given the seriousness and the apparent high frequency of hypoglycaemia following insulin therapy, and the fact that this has not been comprehensively studied, we conducted a scoping review of this important complication, and of other adverse effects of the treatment of hyperkalaemia.

Objectives

We conducted a scoping review to map existing research on this topic and to identify any knowledge gaps. A hybrid approach was used. This included a confirmatory approach for known complications such as hypoglycaemia, as well as an exploratory approach where the included studies were screened for less well-known or unexpected complications.

The following research questions were investigated:

1. What are the reported adverse effects of insulin therapy during the emergency treatment of hyperkalaemia?
2. What is the prevalence of hypoglycaemia?
3. Have there been any other adverse effects reported?
4. What is the timing of adverse effects following therapy?
5. Have studies pre-specified surveillance for adverse effects or was the detection and reporting of adverse effects opportunistic?
6. What are the factors associated with a higher or lower risk of hypoglycaemia? We focused on the doses of insulin and dextrose used, the sequence of administration, the presence of diabetes, and pre-treatment glucose concentrations.

Materials and methods

Protocol and registration

We followed the *P*referred *R*eporting *I*tems for *S*ystematic *R*eviews and *M*eta-analysis–*Sc*oping *R*eviews (PRISMA-ScR) (S1 Checklist). The final protocol was registered prospectively with the Open Science Framework in September 2021 (https://osf.io/x8cs9/).

Eligibility criteria

Research articles were eligible for inclusion if they reported any adverse effects, particularly hypoglycaemia, in adult patients (at least 18 years old), with hyperkalaemia receiving treatment that included insulin therapy. We included randomised controlled trials, prospective and retrospective cohort studies, prospective experimental cross-over studies, case-control studies, cross-sectional studies, and case series. Existing systematic reviews were also included. We excluded studies in paediatric populations, patients not treated in hospital, animal studies and case reports (S1 Table).

Information sources

To identify relevant research, we searched the following bibliographic databases: Medline (PubMed), Embase (Ovid), the Cochrane Library (Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews), CINAHL (EBSCOhost), Africa-Wide Information (EBSCOhost), Web of Science Core Collection (specifically Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index (Clarivate)), LILACS (Virtual Health Library) and Epistemonikos. The search strategy was tailored to each

database, which is available in supporting information. All eligible research reports from 1980 to 12 October 2021, regardless of language, were included. The search strategy was performed by one of the authors (AS), an information specialist at Stellenbosch University. We also searched the conference proceedings of major nephrology congresses, specifically the American Society of Nephrology's Kidney Week, the International Society of Nephrology's World Congress of Nephrology and the European Renal Association-European Dialysis and Transplant Association congress, during the prior 3 years. The reference lists of retrieved publications were also hand-searched for additional relevant articles. A comprehensive search strategy can be found in S2 Table.

Selection of eligible research

The deduplicated search yield was imported into Rayyan screening software (https://rayyan.ai/). Two reviewers (MYC and TH) independently screened all the identified articles' titles and abstracts. Conflicts were resolved by means of discussion and reaching consensus. For those selected to be potentially eligible, we obtained the full-text articles, and these were screened by a single reviewer (MYC). Reasons were provided where studies were excluded during the full-text screening stage (S3 Table).

Data extraction tool and data items

The first reviewer (MYC) developed and pilot-tested the data extraction tool with input from the other authors. The data that we extracted included the study design, type and year of publication, setting, sample size, demographics, comorbid and medication data, definitions of hyperkalaemia and hypoglycaemia, pre-treatment potassium and glucose concentrations, insulin regimen (type, dose, timing of administration and bolus vs. continuous infusion), dextrose administration where applicable (dose and bolus vs. continuous infusion), adverse events (timing, frequency, prespecified vs. opportunistic) and the utilisation of any other hyperkalaemia-specific therapies.

Critical appraisal of individual sources of evidence

The AMSTAR (Assessing the Methodological Quality of Systematic Reviews) 2 tool was used to grade the quality of included systematic reviews as either high, moderate, low, or critically low [11]. This was performed by two reviewers (MYC and AS) in a non-blinded manner.

Data synthesis

We provided a narrative synthesis of the extracted data. This was displayed in table format (S4 Table) and discussions were used to report similarities and differences between studies, as well as identifying gaps in the current evidence base.

Results

Selection of included research

The results of the search strategy and study selection are shown in Fig 1. We included a total of 62 research articles in the scoping review [2, 4, 9, 10, 12–69].

Characteristics of included research

Descriptive results of the primary studies are provided in Table 1. The most common study design was a retrospective cohort study (n = 38 studies); most studies were performed in

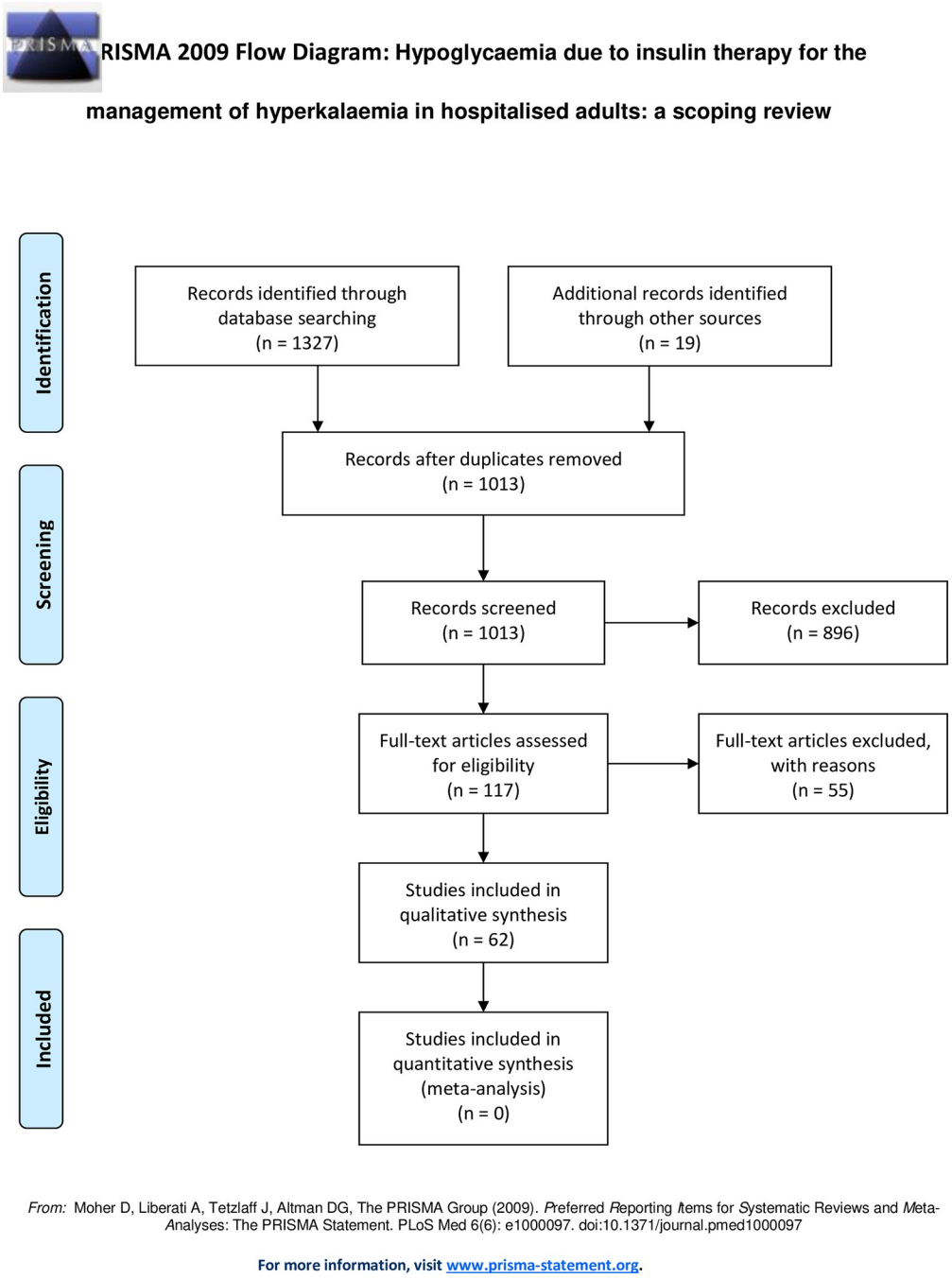

Fig 1. Flow diagram of study selection.

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North America (n = 38 studies); three quarters (n = 48 studies) were conducted from 2015 to 2021, most of which were published articles (n = 45 studies); and the most frequent definitions used for hyperkalaemia and hypoglycaemia were K+ more than 5.0 mmol/L (n = 14 studies) and a glucose concentration less than or equal to 3.9 mmol/L (n = 40 studies), respectively. Table 2 provides a summary of the individual study characteristics. The complete data set can be found as supporting information as S7 Table.

Table 1. Summary of characteristics of included studies.

Items	Summary
Study design	N = 62
Retrospective cohort	38
Prospective cohort	9
Systematic review	5
Randomised control trial	3
Prospective experimental crossover	2
Case series	1
Case-control	1
Not defined	3
Setting (continent)	N = 62
North America	38
Europe	11
Asia	5
Africa	2
Australia	1
Year of publication	N = 62
1988	2
1989	1
1990	1
1993	1
1996	1
1997	1
2001	1
2002	1
2005	1
2006	1
2012	1
2014	2
2015	3
2016	4
2017	7
2018	6
2019	11
2020	10
2021	7
Type of publication	N = 62
Published articles	45
Conference proceedings	17
Range of sample size in studies	N = 15363
Minimum	5
Maximum	1307
Definitions for hyperkalaemia	N = 57
>5.0 mmol/L	14
≥5.1 mmol/L	5
>5.3 mmol/L	2
>5.4 mmol/L	1
≥5.5 mmol/L	6

(*Continued*)

Table 1. (Continued)

Items	Summary
≥6.0 mmol/L	7
>6.1 mmol/L	1
≥7.0 mmol/L	1
Not defined	19
Other[#]	1
Definitions for hypoglycaemia	N = 50
<2.8 mmol/L	1
<3.0 mmol/L	2
<3.3 mmol/L	2
≤3.9 mmol/L	40
Not defined	5
Definitions for severe hypoglycaemia	N = 25
≤2.2 mmol/L	14
≤2.8 mmol/L	11

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Characteristics and critical appraisal of included systematic reviews

We identified five systematic reviews (S5 Table) [2, 4, 67–69]. Two reviews were regarded as being of critically low quality (no registered protocol before commencement of the review could be identified or no list and justification for the exclusion of studies or did not perform a comprehensive search strategy) [2, 68], one review was of moderate quality (two non-critical domain findings) [69] and two of high quality [4, 67].

Synthesis of results

Summary of patient characteristics and pharmacological data. There was a total of 82 treatment arms among the 57 included primary studies, with 23 studies having two treatment arms, one having three treatment arms and 33 having a single treatment arm. Patient characteristics are summarised in Table 2. The total sample size was 15 363 patients. The mean [SD] age was 59.9 [7.4] years; most of the patients were male (n = 6 462 patients, n = 56 treatment arms), with a male-to-female ratio of 1.3:1; and the most frequent comorbidities were kidney failure (n = 5 351 patients) and diabetes mellitus (n = 3 575 patients). Renin-angiotensin-aldosterone system inhibitor use was reported in eight studies (n = 1 539 patients) (S1 Fig). Thirteen studies reported the use of chronic diabetic medication of which insulin therapy (n = 538 patients) was the most frequent (S2 Fig).

The data for insulin and dextrose use has been summarised in Table 2. Insulin dose was reported in 62 treatment arms. The dose could not be calculated for eight treatment arms because a dose range was reported for five treatment arms and an infusion rate (in units/kg/min)—without providing weight—was reported for three treatment arms. Regular insulin was most frequently prescribed (n = 47 treatment arms) at a median dose of 10 units [IQR 10–10 units]; insulin was administered as a bolus in most studies (n = 27 treatment arms) and was co-administered with dextrose in 26 treatment arms. The dextrose dose was available for 61 treatment arms. The dose could not be calculated for three treatment arms because a range was reported for two treatment arms and an infusion rate (mg/kg/min)—without providing weight—was reported for one treatment arm. The median dextrose dose was 25 g [IQR 25–40 g] and was most frequently administered as a bolus (n = 19 treatment arms).

Table 2. Summary of demographic, clinical and pharmacological data for primary included studies.

	Number of treatment arms, n = 82	
Demographic and clinical data		
Total sample size, n	81	15 363
Age (years), mean [SD]	65	59.9 [7.4]
Sex, n		
Male	56	6 462
Not reported	27	–
Male: Female ratio	56	1.3:1
Weight (kg), mean [SD]	31	78 [7.3]
BMI (kg/m^2), mean [SD]	14	27.2 [2.7]
Comorbidities, n		
Diabetes mellitus	46	3 575
Heart failure	2	43
Kidney transplant recipients	2	111
Kidney failure	52	5 351
Acute kidney injury	18	1 003
Chronic kidney disease (non-dialysis)	20	2 781
Chronic dialysis	42	2 254
Pharmacological data		
Insulin		
Overall average dose (units), median [IQR]	62	10 [10–10]
<10 units, median [IQR]	14	5.9 [5.0–8.7]
5–10 units	5	–
≥10 units, median [IQR]	48	10 [10–10]
Type of insulin		
Regular	47	–
Short-acting	5	–
Timing		–
Before dextrose	3	–
With dextrose	26	–
After dextrose	8	–
Infusion rate		–
Bolus	27	–
Continuous	9	–
Continuous infusion rate (min), mean [SD]	9	105 [103]
Dextrose		
Overall average dose (g), median [IQR]	62	25 [25–40]
≤25 g, median [IQR]	40	25 [25–25]
>25 g, median [IQR]	22	50 [40–50]
Infusion rate, %		
Bolus	19	–
Continuous	15	–
Infusion rate (min), median [IQR]	15	22.5 [15–60]
Additional potassium-lowering therapies		
Calcium salts	17	–
Furosemide	21	–
Sodium polystyrene sulphonate	21	–
Salbutamol nebulisation	24	–

(*Continued*)

Table 2. (Continued)

	Number of treatment arms, n = 82	
Intravenous sodium bicarbonate	19	–
Dialysis	4	–

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Additional hyperkalaemia therapies included calcium salts (n = 17 treatment arms), furosemide (n = 21 treatment arms), sodium polystyrene sulphonate (n = 21 treatment arms), salbutamol nebulisations (n = 24 treatment arms), intravenous sodium bicarbonate (n = 19 treatment arms) and dialysis (n = 4 treatment arms) (S3 Fig).

What were the reported adverse effects of insulin therapy during the emergency treatment of hyperkalaemia. Nearly all the primary studies reported prespecified adverse effects (n = 55) while one study reported opportunistic adverse effects [63], and another reported both prespecified and opportunistic adverse effects [21]. Hypoglycaemia was the prespecified adverse effect reported by all primary studies. The opportunistic adverse effects reported by a single study was pulmonary oedema (one patient) and burning/warm sensations in the infusion arm or over the chest when 100 mL of 50% dextrose was administered that promptly subsided once the infusion was complete (10 patients) [21].

What is the prevalence of hypoglycaemia. The prevalence of hypoglycaemia (by any definition) reported by the primary studies was 17.2% [95% CI 16.6–17.8%] while the prevalence of severe hypoglycaemia (by any definition) was 5.4% [95% CI 4.9–5.9%] (Table 3). Prevalence of hypoglycaemia by specific definitions have been summarised in Table 3. The prevalence of hypoglycaemia for retrospective (n = 55 treatment arms) and prospective (n = 22 treatment arms) studies were 17.3% [95% CI 16.7–17.9%] and 15.8% [95% CI 13.4–18.5%], respectively, P = 0.54. The reported prevalence of hypoglycaemia in the systematic reviews ranged from 16.8% to 20.9% (S5 Table).

What was the timing of hypoglycaemia. Forty-three primary studies reported the duration of monitoring for hypoglycaemia, of which half monitored up to six hours following the administration of insulin therapy (S4 Fig). The median timing of hypoglycaemia occurred at 124 minutes [IQR: 102–168 minutes].

What were the factors associated with higher or lower risk of hypoglycaemia. There were no differences in the prevalence of hypoglycaemia when comparing insulin dose (<10 units vs. ≥10 units), rate of insulin administration (continuous vs. bolus), type of insulin (regular vs. short-acting) or timing of insulin administration relative to dextrose (before vs. with

Table 3. Prevalence of hypoglycaemia and severe hypoglycaemia (by any definition and specified definitions).

Prevalence of hypoglycaemia	% [95% CI]
By any definition	17.2 [16.6–17.8]
By specific definitions	
<2.8 mmol/L	8.1 [5.7–11.1]
<3.0 mmol/L	8.6 [6.2–11.6]
<3.3 mmol/L	10.0 [7.9–12.5]
≤3.9 mmol/L	16.9 [16.3–17.5]
Severe hypoglycaemia	
By any definition	5.4 [4.9–5.9]
By specific definitions	
≤2.2 mmol/L	3.8 [3.2–4.4]
≤2.8 mmol/L	6.5 [5.8–7.3]

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Table 4. Comparison of the prevalence of hypoglycaemia by insulin (dose, rate of infusion, type, and timing relative to dextrose) and dextrose (dose and rate of infusion).

Insulin and dextrose	Prevalence of hypoglycaemia (%), median [IQR]	p-value	Prevalence of severe hypoglycaemia (%), mean [SD]	p-value
Insulin				
Dose				
<10 units	10.9 [8.7–19.5]	0.26	3.5 [2.8]	**0.03**
≥10 units	17.5 [8.3–20.5]		5.9 [2.6]	
Rate of infusion				
Bolus	15.8 [6.8–22.2]	0.23	4.9 [3.4]	0.74
Continuous	6.1 [0.0–20.0]		4.0 [4.0]	
Type				
Regular	14.9 [8.7–20.5]	0.26	4.5 [3.0]	0.64
Short-acting	8.3 [6.1–15.8]		3.4 [3.1]	
Timing relative to dextrose				
Before	20.0 [2.1–75.0]	0.68	None	0.91
With	17.6 [3.3–28.6]		4.2 [2.4]	
After	13.5 [3.4–21.1]		4.0 [4.4]	
Dextrose				
Dose				
≤25g	17.1 [8.7–20.9]	0.52	5.5 [3.4]	0.19
>25g	12.5 [8.3–19.7]		4.0 [2.9]	
Rate of infusion				
Bolus	19.5 [11.1–27.8]	**0.02**	5.3 [3.4]	0.36
Continuous	3.3 [0.0–20.0]		3.2 [3.1]	

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vs. after dextrose) (Table 4). However, lower insulin doses were associated with reduced prevalence of severe hypoglycaemia [3.5% vs. 5.9%, P = 0.02]. There was no difference regarding the reduction in serum K+ with lower vs. standard/high insulin doses [-0.81 mmol/L vs. -0.90 mmol/L, respectively, P = 0.18] (S5 Fig).

There was no difference regarding the prevalence of hypoglycaemia by dextrose dose (≤25 g vs. >25 g); however, prevalence was lower when dextrose was administered as a continuous infusion compared with bolus administration [3.3% vs. 19.5%, P = 0.02] (Table 4).

For comorbidities, the prevalence of hypoglycaemia was lower in treatment arms that reported this outcome in the sub-population of patients with diabetes (n = 12 treatment arms) compared to those without (n = 8 treatment arms), although this did not reach statistical significance [11.2% vs. 20.0%, P = 0.46] (S6 Fig). Also, the prevalence of hypoglycaemia was higher in treatment arms that reported this outcome in the sub-population of patients with kidney failure (n = 34 treatment arms) but was not statistically significant [19.6% vs. 10.2%, P = 0.70]. The prevalence was 22.7% for kidney transplant recipients.

Studies reporting additional hyperkalaemia therapies had lower prevalence of hypoglycaemia [14.3% vs. 18.3%, P = 0.03] (S7 Fig) as well as greater reductions in K+ [-1.0 mmol/L vs. -0.83 mmol/L, P = 0.03] when compared to studies where no additional therapies were used (S8 Fig).

Sixteen primary studies performed regression analysis [10, 12, 15, 23, 26, 29, 32, 34, 37, 46, 49, 53, 57, 59, 62, 65]. The most common predictors of hypoglycaemia were pre-treatment serum glucose concentration (n = 13 studies), insulin dose (n = 8 studies), kidney failure (n = 5 studies) and diabetes (n = 4 studies). Other predictors included weight/BMI, age, sex, and treatment in the emergency department (S6 Table).

One systematic review that we judged to be of critically low quality, performed meta-analyses and reported that alternative insulin dosing (defined as < 10 units) had lower odds associated with hypoglycaemia and severe hypoglycaemia [68].

Discussion

This scoping review is the first comprehensive scoping review of hypoglycaemia and other adverse effects following the emergency management of hyperkalaemia. We identified 62 research articles, with most reporting on hypoglycaemia as a prespecified adverse effect and most performed during the past six years. The overall prevalence of hypoglycaemia for primary studies by any definition was 17.2% and ranged from 0% to 75%. This wide range may be due to differences in the definitions for hypoglycaemia, differences in the study populations and the insulin/dextrose regimens. For systematic reviews, the overall prevalence of hypoglycaemia had a narrow range (16.8% to 20.9%). Variation in the size of the total number of patients of included primary studies may have impacted on the observed prevalence with larger studies reporting the lowest prevalence. Another factor was the difference in the duration of monitoring for hypoglycaemia following insulin therapy which ranged from 60 minutes to 480 minutes. A study that only monitored for 60 minutes following insulin reported no episodes of hypoglycaemia [67]. However, since most systematic reviews only included prospective studies that actively monitored for hypoglycaemia, it is unlikely that episodes of hypoglycaemia were missed.

Hypoglycaemia occurred at an average of two hours following insulin therapy. It is recommended that patients with hyperkalaemia treated with insulin therapy should be monitored for up to six hours following therapy since the glucose lowering effect of insulin is prolonged in patients with kidney failure [3]. This finding is especially important since treatment is often administered in busy emergency departments where close monitoring for hypoglycaemia may be challenging.

The dose, type, rate of infusion and administration of insulin relative to dextrose were not associated with hypoglycaemia in our scoping review. However, a systematic review with meta-analysis that we judged to be of critically low quality reported a reduced prevalence of hypoglycaemia when lower doses of insulin were compared with standard doses [68]. Since there was no difference in efficacy regarding the reduction of the serum K+ with lower doses of insulin, and lower doses having a reduced risk of severe hypoglycaemia, it seems that lower doses of insulin (5 units or 0.1 units/kg) should be considered for the emergency management of hyperkalaemia.

Although a higher dextrose dose was not associated with a lower prevalence of hypoglycaemia, continuous infusion was. A theoretical regimen suggested that 60 g of 10% dextrose be infused over one hour [5]. This would require a volume of 600 mL. However, pulmonary oedema was described in a patient with kidney failure and hypertensive heart disease following 100 mL of 50% dextrose administered as a bolus [21]. Since hyperkalaemia frequently occurs in patients with kidney failure [1], decisions regarding the rate and volume of dextrose utilised should include the assessment of the patient's volume and cardiac status.

We found that primary studies which included the use of additional hyperkalaemia therapies had a lower prevalence of hypoglycaemia. The reasons for this were unclear. There were no differences between studies that did and did not report additional therapies regarding pre-treatment serum K+, pre-treatment serum glucose concentrations, type, doses, or rate of infusion of insulin and dextrose, diabetes status and kidney failure. However, in systematic reviews, one study reported less episodes of hypoglycaemia when salbutamol nebulisations were added to insulin therapy [14], and another reported no episodes when variable

combinations of salbutamol and sodium bicarbonate were added to insulin [51]. Sympathetic stimulation by salbutamol may stimulate gluconeogenesis counteracting the hypoglycaemic effect of insulin.

The most common predictor of hypoglycaemia was a lower pre-treatment serum glucose concentration. This may explain why some primary studies identified diabetes status as having a reduced risk of hypoglycaemia [15, 23, 46, 49]. Other predictors included insulin dose and kidney failure. Although we found higher prevalence rates of hypoglycaemia in patients with kidney failure and lower rates in those with diabetes, they were not statistically significant; however, the total number of treatment arms included suggests that these analyses were likely underpowered. Therefore, awareness of the pre-treatment serum glucose concentration and kidney function may be important prior to prescribing insulin therapy as these factors may help to inform the prescription so that the risk of hypoglycaemia can be reduced.

Limitations

This scoping review has some limitations. Included studies with small sample sizes may have under- or overestimated hypoglycaemia prevalence. A few studies monitored for hypoglycaemia only up to 60 minutes. These studies may have underreported the prevalence of hypoglycaemia since this complication frequently occurs more than one hour following insulin therapy. Most of the studies were retrospective in design and hypoglycaemia was the only prespecified adverse effect. Therefore, there may be underreporting of other opportunistic adverse effects. The accuracy of some of the serum glucose measurements at the defined threshold values may have affected the prevalence of hypoglycaemia, especially when bedside capillary blood glucose measurements were performed [70]. Insulin and dextrose doses were not explicitly reported by some primary studies.

Conclusions

This is the first comprehensive scoping review of the frequency of adverse effects following therapy with insulin for the emergency management of hyperkalaemia. Hypoglycaemia, the most concerning complication of this therapy, remains a common adverse effect but may be reduced by adapting the prescription of both insulin therapy. Most of the primary studies included in this review were retrospective in design; future randomised trials should focus on identifying the optimal regimen of insulin therapy to mitigate the risk of hypoglycaemia, while still effectively reducing K+, to inform treatment guidelines and clinical practice.

Supporting information

S1 Checklist. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
(PDF)

S1 Table. Inclusion and exclusion criteria.
(PDF)

S2 Table. Search strategy of databases.
(PDF)

S3 Table. List of excluded studies.
(PDF)

S4 Table. Individual primary study characteristics. *Kidney failure includes acute kidney injury, chronic kidney disease and end-stage kidney disease. †RCS, retrospective cohort study;

‡PCOS, Prospective cross-over study; §PCS, prospective cohort study; ||RCT, Randomised control trial; ¶CC, case-control study; #CS, Case series; **K, Potassium.
(PDF)

S5 Table. Included systematic reviews.
(PDF)

S6 Table. Predictors of hypoglycaemia by primary studies that performed regression analysis. All predictors included were statistically significant, $P<0.05$.
(PDF)

S7 Table. Data set.
(XLS)

S1 Fig. Number of patients prescribed drugs associated with hyperkalaemia.
(TIF)

S2 Fig. Number of patients prescribed chronic anti-diabetic medication.
(TIF)

S3 Fig. Number of studies reporting additional hyperkalaemia therapies.
(TIF)

S4 Fig. Duration of monitoring for hypoglycaemia.
(TIF)

S5 Fig. Comparison of the average reduction in serum potassium concentration with <10 units vs. ≥10 units of insulin.
(TIF)

S6 Fig. Rates of hypoglycaemia by diabetic status.
(TIF)

S7 Fig. Rates of hypoglycaemia by additional hyperkalaemia therapies.
(TIF)

S8 Fig. Average reduction in serum potassium concentration by additional hyperkalaemia therapies.
(TIF)

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S1 Appendix. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4,5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5,6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6,7
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	7
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	8
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	8
RESULTS			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	9
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	9
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	12
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	12
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	12
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	16
Limitations	20	Discuss the limitations of the scoping review process.	19
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	19
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	20

S2A Table. Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Participants	Adults (≥ 18 years old)	Paediatric patients
Intervention / exposure	Insulin and glucose	
Language	All	
Study designs	Systematic reviews Randomised control trials Cohort studies Case-control studies Case series Cross-sectional studies	Case reports
Publication type	Peer-reviewed publications Relevant systematic reviews Conference proceedings (limited to the last 3-years)	
Setting	Hospitalised	Outpatients
Time period	January 1980 to 12 October 2021	
Outcomes	Any reported adverse effects following therapy with insulin and glucose for the treatment of hyperkalaemia	

S2B Table. Search strategy of databases

Database	Search terms
Medline (PubMed)	#1 "adverse effects"[MeSH Subheading] OR "complications"[MeSH Subheading] OR "deficiency"[MeSH Subheading] OR "safe"[Title/Abstract] OR "safety"[Title/Abstract] OR "side effect"[Title/Abstract] OR "side effects"[Title/Abstract] OR "undesirable effect"[Title/Abstract] OR "undesirable effects"[Title/Abstract] OR "treatment emergent"[Title/Abstract] OR "tolerability"[Title/Abstract] OR "toxicity"[Title/Abstract] OR "ADRS"[Title/Abstract] OR ("adverse"[Title/Abstract] AND ("effect"[Title/Abstract] OR "effects"[Title/Abstract] OR "reaction"[Title/Abstract] OR "reactions"[Title/Abstract] OR "event"[Title/Abstract] OR "events"[Title/Abstract] OR "outcome"[Title/Abstract] OR "outcomes"[Title/Abstract])) #2 "Hypoglycemia"[Mesh] OR "hypoglycaemia"[Title/Abstract] OR "hypoglycemia"[Title/Abstract] OR "low blood sugar"[Title/Abstract] OR "low blood glucose"[Title/Abstract] #3 #1 OR #2 #4 “Hyperkalemia” [MeSH] OR hyperkalemia [Title/Abstract] OR hyperkalaemia [Title/Abstract] OR “hyperpotassaemia” [Title/Abstract] OR “hyperpotassemia” [Title/Abstract] #5 #3 AND #4 #6 "Insulin"[Mesh] OR insulin [Title/Abstract] #7 "Glucose"[Mesh] OR glucose [Title/Abstract] OR dextrose [Title/Abstract] #8 #6 AND #7 #9 #5 AND #8
Embase (Ovid)	1. adverse drug reaction/ 2. (complication* or deficiency or safety or toxicity or tolerability).tw. 3. exp drug safety/ 4. ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw. 5. 1 or 2 or 3 or 4 6. hypoglycemia/ 7. (hypoglycaemia or hypoglycemia).tw. 8. ("low blood sugar" or "low blood glucose").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 9. 5 or 6 or 7 or 8 10. hyperkalemia/ 11. (hyperkalemia or hyperkalaemia).tw. 12. hyperpotassaemia.mp. 13. hyperpotassemia.mp. 14. 10 or 11 or 12 or 13 15. 9 and 14 16. insulin/ or insulin.mp. 17. glucose/ or glucose.mp. 18. dextrose.mp. 19. 17 or 18 20. 16 and 19 21. 15 and 20
Cochrane Library (CENTRAL AND CDSR)	#1 MeSH descriptor: [Long Term Adverse Effects] explode all trees #2 (complications):ti,ab,kw #3 MeSH descriptor: [Deficiency Diseases] explode all trees #4 (safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR ADRS):ti,ab,kw #5 (adverse AND effect):ti,ab,kw #6 (adverse AND effects):ti,ab,kw

	#7 (adverse AND reaction):ti,ab,kw #8 (adverse AND reactions):ti,ab,kw #9 (adverse AND event):ti,ab,kw #10 (adverse AND events):ti,ab,kw #11 (adverse AND outcome):ti,ab,kw #12 (adverse AND outcomes):ti,ab,kw #13 MeSH descriptor: [Hypoglycemia] explode all trees #14 (hypoglycaemia OR hypoglycemia OR "low blood sugar" OR "low blood glucose"):ti,ab,kw #15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 #16 MeSH descriptor: [Hyperkalemia] explode all trees #17 (hyperkalemia OR hyperkalaemia OR hyperpotassaemia OR hyperpotassemia):ti,ab,kw #18 #16 OR #17 #19 MeSH descriptor: [Insulins] explode all trees #20 (insulin):ti,ab,kw #21 #19 OR #20 #22 MeSH descriptor: [Glucose] explode all trees #23 (glucose):ti,ab,kw #24 (dextrose):ti,ab,kw #25 #22 OR #23 OR #24 #26 #21 AND #25 #27 #15 AND #18 AND #26
Africa-wide information (EBSCOHost)	S23. S15 AND S17 AND S22 S22. S19 AND S21 S21. TI (glucose or dextrose) OR AB (glucose or dextrose) S20. SM glucose S19. TI insulin OR AB insulin S18. SM insulin S17. TI (hyperkalemia OR hyperkalaemia OR hyperpotassaemia OR hyperpotassemia) OR AB (hyperkalemia OR hyperkalaemia OR hyperpotassaemia OR hyperpotassemia) S16. SM hyperkalemia S15. S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S14 S14. TI (hypoglycaemia OR hypoglycemia OR "low blood sugar" OR "low blood glucose") OR AB (hypoglycaemia OR hypoglycemia OR "low blood sugar" OR "low blood glucose") S13. SM hypoglycemia S12. TI (adverse AND outcomes) OR AB (adverse AND outcomes) S11. TI (adverse AND outcome) OR AB (adverse AND outcome) S10. TI (adverse AND events) OR AB (adverse AND events) S9. TI (adverse AND event) OR AB (adverse AND event) S8. TI (adverse AND reactions) OR AB (adverse AND reactions) S7. TI (adverse AND reaction) OR AB (adverse AND reaction) S6. TI (adverse AND effects) OR AB (adverse AND effects) S5. TI (adverse AND effect) OR AB (adverse AND effect) S4. TI (safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR ADRS) OR AB (safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR ADRS) S3. SM deficiency S2. SM complications S1. SM "adverse effects"
Web of Science core collection (Science	#24 AND #15 AND #18 #21 OR #22 #19 OR #20 glucose or dextrose (Title) or glucose or dextrose (Abstract)

Citation Index Expanded, Social Science Citation Index, Conference Proceedings Citation Index [Clarivate])	glucose (Topic) insulin (Title) or insulin (Abstract) insulin (Topic) #16 OR #17 hyperkalemia OR hyperkalaemia OR hyperpotassaemia OR hyperpotassemia (Title) or hyperkalemia OR hyperkalaemia OR hyperpotassaemia OR hyperpotassemia (Abstract) TS=(hyperkalemia) #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 hypoglycaemia OR hypoglycemia OR "low blood sugar" OR "low blood glucose" (Title) or hypoglycaemia OR hypoglycemia OR "low blood sugar" OR "low blood glucose" (Abstract) hypoglycemia (Topic) adverse AND outcomes (Title) or adverse AND outcome (Abstract) adverse AND outcome (Title) or adverse AND outcomes (Abstract) adverse AND events (Title) or adverse AND events (Abstract) adverse AND event (Title) or adverse AND event (Abstract) adverse AND reactions (Title) or adverse AND reactions (Abstract) adverse AND reaction (Title) or adverse AND reaction (Abstract) adverse AND effects (Title) or adverse AND effects (Abstract) adverse AND effect (Title) or adverse AND effect (Abstract) safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR ADRS (Title) or safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR ADRS (Abstract) deficiency (Topic) complications (Topic) "adverse effects" (Topic)
LILACS (Virtual Health Library)	Search 1 Adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia [Words] and hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia [Words] and insulin [Words] Search 2 Adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia [Words] and hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia [Words] and glucose OR dextrose [Words]
Epistemonikos	Search 1 (title:((title:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia) OR abstract:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia)) AND (title:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia) OR abstract:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia)) AND (title:(glucose OR dextrose) OR abstract:(glucose OR dextrose))) OR abstract:((title:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia) OR abstract:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia)) AND (title:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia) OR abstract:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia)) AND (title:(glucose OR dextrose) OR abstract:(glucose OR dextrose)))) Search 2

	(title:((title:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia) OR abstract:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia)) AND (title:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia) OR abstract:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia)) AND (title:(insulin) OR abstract:(insulin))) OR abstract:((title:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia) OR abstract:(adverse effects OR adverse events OR adverse reactions OR adverse outcomes OR hypoglycemia OR hypoglycaemia)) AND (title:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia) OR abstract:(hyperkalemia OR hyperkalaemia OR hyperpotassemia OR hyperpotassaemia)) AND (title:(insulin) OR abstract:(insulin))))

S2C Table. List of excluded studies

Study	Reason for exclusion
Ahmad et al. 2010	No adverse effects reported
Al-Sharefi et al. 2019	Letter
Alfonzo et al. 2006	Review
Aljabri et al. 2017	Full text used
Allon et al. 1993	No baseline hyperkalaemia
Alsulami et al. 2019	Full text used
Boughton et al. 2019	Letter
Boughton et al. 2019	Duplicate
Broz et al. 2018	Letter
Broz et al. 2019	Letter
Centeno et al. 2017	Not a hyperkalaemia-specific study
Depret et al. 2019	Review
Doshi et al. 2016	Review
Driver et al. 2017	Multiple causes of hypoglycaemia
Effa et al. 2017	Review
Evans et al. 2004	Review
Farina et al. 2016	Full text used
Fischer et al. 1986	Multiple causes of hypoglycaemia
Goksu et al. 2003	No adverse effects reported
Groene et al. 2017	Review
Hendra et al. 2016	No adverse effects reported
Humphrey et al. 2019	Full text used
Jamal et al. 2018	Information sparse
Janjua et al. 2011	Paediatric study
Kraft et al. 2005	Review
Kraft et al. 2006	Letter
Krishnan 2002	Review
LaRue et al. 2015	Full text used
Li et al. 2014	Review
Liu et al. 2019	Review
Long et al. 2019	Letter
Macedo et al. 2017	No adverse effects reported
Mastroianni et al. 2017	Adverse effects related to insulin not clear
Maxwell et al. 2013	Review
McVeigh 2003	Review
Moussavi et al. 2019	Review
Moussavi et al. 2021	Full text used
Mustafa et al. 2014	Editorial
Palaka et al. 2017	Only resins investigated
Paparella et al. 2018	Letter
Peacock et al. 2016	Data unavailable
Peacock et al. 2020	No insulin-based therapy
Putcha et al. 2007	Review
Rajendran et al. 2014	Survey
Raymond et al. 2010	Review
Rossignol et al. 2016	Guideline
Sacchetti et al. 1999	Dialytic therapy only
Sridhar et al. 2018	Insulin for hyperglycaemia
Tabatabai et al. 2014	Survey
Tzamaloukas et al. 1987	Insulin for hyperglycaemia
Verdier et al. 2020	Full text used
Xia et al. 2010	Rates of hypoglycaemia not reported
Yorifuji et al. 2013	Multiple causes of hypoglycaemia
Zahoor et al. 2012	Hyperkalaemia post-parathyroidectomy
No author	Unidentifiable paper

S2D Table. Individual primary study characteristics

Author	Year	Study design	Sample	Age	Male	KF*	Definition hyperka	Definition hypogly	Duration of monitor	Pretreatment [K+]	Pretreatment [glucos	Insulin (IU)	Insulin (IU/kg)	Dextrose (g)	[K+] reduction, mM	% Hypoglycaemia
Aljabri (12)	2019	RCS	90	62	48	Yes	>5.0	≤3.9	6	6	7	10	–	25	N/D	22
Aljabri (13)	2021	RCS	521	62	271	Yes	>5.0	≤3.9	6	6	8	10	–	25	N/D	2
Allon (14)	1990	PCOS	10	57	N/D	Yes	>5.0	N/D	1	6	5	10	–	25	-1.21	20
Allon (14)	1990	PCOS	12	57	N/D	Yes	>5.0	N/D	1	6	5	10	–	25	-0.65	75
Apel (9)	2014	RCS	221	51	18	Yes	N/D	<3.3	6	N/D	6	10	–	25	N/D	13
Beltrami-Moreira (15)	2020	PCS	160	68	78	Yes	N/D	≤3.9	12	N/D	N/D	5–10	N/D	N/D	N/D	18
Binz (16)	2020	RCS	1291	62	752	Yes	N/D	≤3.9	N/D	6	8	–	–	25	N/D	18
Blumberg (17)	1988	PCS	10	58	5	Yes	N/D	N/D	N/D	6	5	–	5u/kg/min	5mg/kg /min	-0.90	50
Boughton (18)	2019	RCS	662	71	617	Yes	N/D	≤3.9	N/D	6	6	10	–	20	-0.60	18
Brown (19)	2018	RCS	264	56	168	Yes	>5.0	≤3.9	8	6	9	8	0.1	24	-0.60	7
Brown (19)	2018	RCS	69	57	64	Yes	>5.0	≤3.9	8	6	9	9	–	26	-0.60	16
Chittineni (20)	2019	RCS	61	49	N/D	N/D	N/D	≤3.9	N/D	N/D	N/D	–	–	N/D	N/D	74
Chothia (21)	2014	RCT	10	40	5	Yes	>5.0	<3.0	N/D	6	6	10	–	50	-0.83	20
Coca (10)	2017	RCS	164	72	6	Yes	≥6.0	≤3.9	8	7	6	10	–	50	-1.37	6
Coca (22)	2017	CC	30	76	18	Yes	N/D	N/D	4	7	7	10	–	50	-0.86	10
Coca (22)	2017	CC	30	76	18	Yes	N/D	N/D	4	7	8	10	–	50	-0.82	3

Author	Year	Study design	Sample	Age	Male	KF*	Definition hyperka	Definition hypogly	Duration of monitor	Pretreatment [K+]	Pretreatment [glucos	Insulin (IU)	Insulin (IU/kg)	Dextrose (g)	[K+] reduction, mM	% Hypoglycaemia
Crnobrnja (23)	2020	RCS	421	71	60	Yes	≥6.0	≤3.9	6	N/D	7	10	–	25	N/D	21
Diveley (24)	2021	RCS	90	N/D	N/D	Yes	>5.0	≤3.9	N/D	N/D	N/D	10	–	N/D	N/D	17
Diveley (24)	2021	RCS	49	N/D	N/D	No	>5.0	≤3.9	N/D	N/D	N/D	10	–	N/D	N/D	10
Dixon (25)	2016	RCS	57	71	N/D	N/D	N/D	<4.0	N/D	N/D	N/D	–	–	N/D	N/D	30
Dixon (25)	2016	RCS	59	69	N/D	N/D	N/D	<4.0	N/D	N/D	N/D	–	–	N/D	N/D	12
Do (26)	2019	RCS	1156	61	682	Yes	>5.0	≤3.9	N/D	6	7	0.1 Iu/kg	0.105	N/D	N/D	18
Driver (27)	2016	RCS	433	N/D	N/D	N/D	>5.3	<2.8	2	N/D	N/D	10	–	34	N/D	8
Farina (28)	2018	RCS	120	60	69	Yes	>5.0	≤3.9	4	7	7	10	–	25	-1.00	16
Farina (28)	2018	RCS	120	62	61	Yes	>5.0	≤3.9	4	6	6	10	–	50	-1.10	8
Garcia (29)	2018	RCS	309	59	219	Yes	≥5.1	≤3.9	6	6	9	10	–	50	-0.90	11
Garcia (29)	2018	RCS	92	62	63	Yes	≥5.1	≤3.9	6	6	8	5	–	19	-0.81	9
Hain (30)	2020	N/D	105	62	N/D	Yes	N/D	≤3.9	3	6	7	10	–	50	-1.10	14
Humphrey (31)	2020	RCS	110	56	N/D	Yes	≥5.5	<4.0	6	6	N/D	–	–	N/D	-0.89	23
Humphrey (32)	2021	RCS	1284	72	804	Yes	≥5.5	<4.0	6	6	8	10	–	25	-0.86	19
Jacob (33)	2019	RCS	172	63	154	Yes	≥5.1	≤3.9	24	7	5	10	0.11	25	-2.10	20
Keeney (34)	2019	RCS	295	60	178	Yes	N/D	≤3.9	6	7	7	10	–	2	-1.13	16

Author	Year	Study design	Sample	Age	Male	KF*	Definition hyperka	Definition hypogly	Duration of monitor	Pretreatment [K+]	Pretreatment [glucos	Insulin (IU)	Insulin (IU/kg)	Dextrose (g)	[K+] reduction, mM	% Hypoglycaemia
Keeney (34)	2019	RCS	147	65	76	Yes	N/D	≤3.9	6	7	7	5	–	2	-1.17	6
Kim (35)	1996	PCOS	8	52	6	Yes	>6.1	N/D	1	6	6	50	6 u/kg/min	20	-1.10	0
Kocoglu (36)	2002	PCS	14	53	10	No	≥8.0	N/D	N/D	N/D	N/D	25	–	50	-0.08	0
Kocoglu (36)	2002	PCS	22	52	14	No	≥7.0	N/D	N/D	N/D	N/D	50	–	100	-1.78	36
Konowitz (37)	2019	RCS	1307	N/D	N/D	N/D	N/D	≤3.9	N/D	6	N/D	–	–	N/D	N/D	18
LaRue (38)	2017	RCS	542	62	272	Yes	>5.0	≤3.9	5	6	8	10	–	39	-1.00	29
LaRue (38)	2017	RCS	133	60	86	Yes	>5.0	≤3.9	5	6	7	5	–	34	-1.00	20
Lane (40)	1989	PCS	10	61	5	Yes	N/D	N/D	6	7	8	10	–	40	-1.00	20
Lane (40)	1989	PCS	10	62	4	Yes	N/D	N/D	6	7	7	10	–	40	-1.50	0
Lim (41)	2019	RCS	96	N/D	N/D	N/D	≥5.5	≤3.9	12	N/D	N/D	–	–	N/D	N/D	19
Ljutic (42)	1993	PCS	9	N/D	5	Yes	>5.0	<3.0	1	6	6	10	–	25	-0.76	22
Macmaster (43)	2017	N/D	100	N/D	N/D	N/D	≥5.1	≤3.9	6	N/D	N/D	10	–	N/D	N/D	23
Macmaster (44)	2018	N/D	146	N/D	N/D	N/D	≥5.1	≤3.9	6	N/D	N/D	–	–	50	N/D	10
Macmaster (44)	2018	N/D	225	N/D	N/D	N/D	≥5.1	≤3.9	6	N/D	N/D	10	–	25	N/D	21
Mahajan (45)	2001	PCS	15	N/D	N/D	N/D	≥6.0	<3.3	6	7	N/D	–	–	N/D	-0.80	7
Mansour (46)	2019	RCS	142	N/D	N/D	Yes	>5.4	≤3.9	6	N/D	N/D	–	–	N/D	N/D	18

Author	Year	Study design	Sample	Age	Male	KF*	Definition hyperka	Definition hypogly	Duration of monitor	Pretreatment [K+]	Pretreatment [glucos	Insulin (IU)	Insulin (IU/kg)	Dextrose (g)	[K+] reduction, mM	% Hypoglycaemia
McNicholas (47)	2017	RCS	63	50	41	Yes	≥6.0	≤3.9	6	7	10	5–10	–	25	N/D	11
McNicholas (47)	2017	RCS	76	56	53	Yes	≥6.0	≤3.9	6	7	7	5–10	–	25	-0.57(10	29
Meloy (48)	2021	RCS	128	N/D	N/D	Yes	≥5.5	≤3.9	6	N/D	N/D	5–10	–	2	N/D	42
Moussavi (49)	2020	RCS	223	60	115	Yes	>5.0	≤3.9	12	6	6	5	0.07	25	-0.94	11
Moussavi (49)	2020	RCS	477	62	259	Yes	>5.0	≤3.9	12	6	8	10	0.14	25	-1.11	18
Mushtaq (50)	2006	PCS	5	51	N/D	Yes	≥6.0	N/D	6	7	8	10	–	25	-1.10	0
Mushtaq (50)	2006	PCS	5	52	N/D	Yes	≥6.0	N/D	6	7	8	10	–	25	-0.80	0
Ngugi (51)	1997	RCT	10	N/D	N/D	Yes	>5.0	N/D	8	N/D	7	10	–	25	-0.90	0
Ngugi (51)	1997	RCT	10	N/D	N/D	Yes	>5.0	N/D	8	N/D	5	10	–	25	-1.39	20
Ngugi (51)	1997	RCT	10	N/D	N/D	Yes	>5.0	N/D	8	N/D	7	10	–	25	-1.19	0
Peacock (52)	2018	PCS	130	56	124	Yes	≥5.5	N/D	4	6	N/D	–	–	N/D	-1.00	6
Pearson (53)	2021	RCS	182	64	108	Yes	N/D	≤3.9	6	6	8	10	–	25	-0.60	19
Pearson (53)	2021	RCS	204	65	125	Yes	N/D	≤3.9	6	6	8	10	–	25	-0.90	18
Pierce (54)	2015	RCS	78	58	71	Yes	≥6.0	≤3.9	8	6	N/D	10	–	25	-1.08	17
Pierce (54)	2015	RCS	71	62	63	Yes	≥6.0	≤3.9	8	6	N/D	5	–	25	-1.10	20
Rafique (55)	2020	RCT	15	48	7	Yes	≥6.0	≤3.9	N/D	7	6	5	–	N/D	-0.60	20

Author	Year	Study design	Sample	Age	Male	KF*	Definition hyperka	Definition hypogly	Duration of monitor	Pretreatment [K+]	Pretreatment [glucos	Insulin (IU)	Insulin (IU/kg)	Dextrose (g)	[K+] reduction, mM	% Hypoglycaemia
Schafers (56)	2012	RCS	219	53	15	Yes	≥6.0	≤3.9	6	N/D	7	5–10	N/D	0–50	N/D	9
Scott (57)	2018	RCS	409	57	N/D	Yes	>5.3	≤3.9	3	6	6	10	–	40	N/D	17
Szwak (58)	2017	RCS	141	N/D	N/D	Yes	N/D	N/D	N/D	N/D	N/D	–	–	N/D	-0.80	26
Tee (59)	2020	RCS	132	63	19	Yes	(≥6.5 or	<4.0	6	6	6	10	–	20–25	-0.77	21
Tran (60)	2020	PCS	225	59	147	Yes	≥5.1	≤3.9	6	6	9	10	0.12	25	-0.73	21
Tran (60)	2020	PCS	145	57	85	Yes	≥5.1	≤3.9	6	6	10	7	0.09	25	-0.95	10
Verdier (61)	2021	RCS	87	61	48	Yes	>5.0	≤3.9	6	6	8	5	–	44	-0.80	9
Verdier (61)	2021	RCS	87	63	52	Yes	>5.0	≤3.9	6	6	8	10	–	47	-0.70	20
Wheeler (62)	2016	RCS	66	56	37	Yes	N/D	≤3.9	24	6	9	10	–	50	-1.35	20
Wheeler (62)	2016	RCS	66	62	41	Yes	N/D	≤3.9	24	6	8	7	0.1	50	-1.34	11
Williams (63)	1988	CS	N/D	39	2	Yes	N/D	N/D	N/D	7	N/D	14	–	20	N/D	N/D
Wu (64)	2015	RCS	191	61	16	Yes	N/D	≤3.9	6	N/D	8	10	–	25	N/D	14
Yang (65)	2019	RCS	62	67	40	Yes	≥5.5	≤3.9	24	6	6	10	0.12	50	-0.80	26
Yang (65)	2019	RCS	72	71	46	Yes	≥5.5	≤3.9	24	6	7	10	0.12	25	-0.90	22
Zuern (66)	2020	RCS	90	59	62	Yes	>5.0	≤3.9	4	6	7	10	0.11	25	-0.80	28
Zuern (66)	2020	RCS	75	61	44	Yes	>5.0	≤3.9	4	6	7	9	0.1	25	-0.60	13

*Kidney failure includes acute kidney injury, chronic kidney disease and end-stage kidney disease. †RCS, retrospective cohort study; ‡PCOS, Prospective cross-over study; §PCS, prospective cohort study; ǁRCT, Randomised control trial; ¶CC, case-control study; #CS, Case series; **K, Potassium.

S2E Table. Included systematic reviews

Author name	Year of publication	Aim	Eligibility criteria	No. of studies that included insulin	Reported adverse events	Quality (AMSTAR)
Batterink et al. (67)	2015	Benefits and harms of pharmacological treatments used in the acute management of hyperkalaemia in adults and evaluated the therapies that reduce serum potassium as well as those that prevent complications of hyperkalaemia.	Adults (aged 18 years and over) with hyperkalaemia, defined as serum potassium concentration >4.9 mmol/L, to receive pharmacological therapy to reduce serum potassium or to prevent arrhythmias.	3	14 of 67 patients with hypoglycaemia (20.9%)	High
Harel et al. (2)	2016	Review data in the literature to determine the optimal dose and route of administration of insulin in the management of emergency hyperkalaemia.	Articles were eligible for inclusion if they reported on using insulin in the management	11	22 of 117 patients with hypoglycaemia (18.8%)	Critically low
Varallo et al. (70)	2019	To evaluate the efficacy, effectiveness, and safety of hyperkalaemia pharmacotherapies.	The population included patients with hyperkalaemia (without restrictions for age, sex, or current or previous past medical history) receiving hyperkalaemia treatment compared with placebo, no treatment, or another comparator.	5	Two patients with hypoglycaemia), One patient with pulmonary oedema)	Moderate

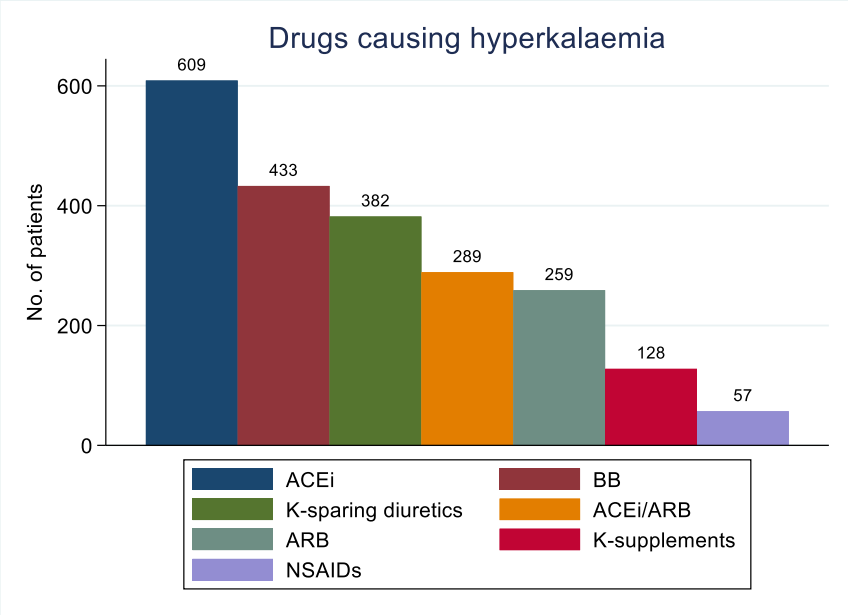
Author name	Year of publication	Aim	Eligibility criteria	No. of studies that included insulin	Reported adverse events	Quality (AMSTAR)
Mahoney et al. (68)	2005	To review randomised evidence informing the acute emergency management of hyperkalaemia.	Studies reporting pharmacological or other interventions to treat non-neonatal humans with hyperkalaemia, reporting on clinically important outcomes, or serum potassium levels within the first six hours of administration.	4	14 of 83 patients with hypoglycaemia (16.9%)	High
Moussavi et al. (69)	2021	To determine the impact of alternative insulin dosing on hypoglycaemia and potassium reduction in patients with hyperkalaemia.	Patients treated with standard (10 units) or alternative (<10 units) insulin	10	Low dose insulin: 124 of 1084 patients with hypoglycaemia (11.4%); Standard dose insulin: 452 of 2353 patients with hypoglycaemia (19.2%); Total 576 of 3437 patients with hypoglycaemia (16.8%)	Critically low

S2F Table. Predictors of hypoglycaemia by primary studies that performed regression analysis

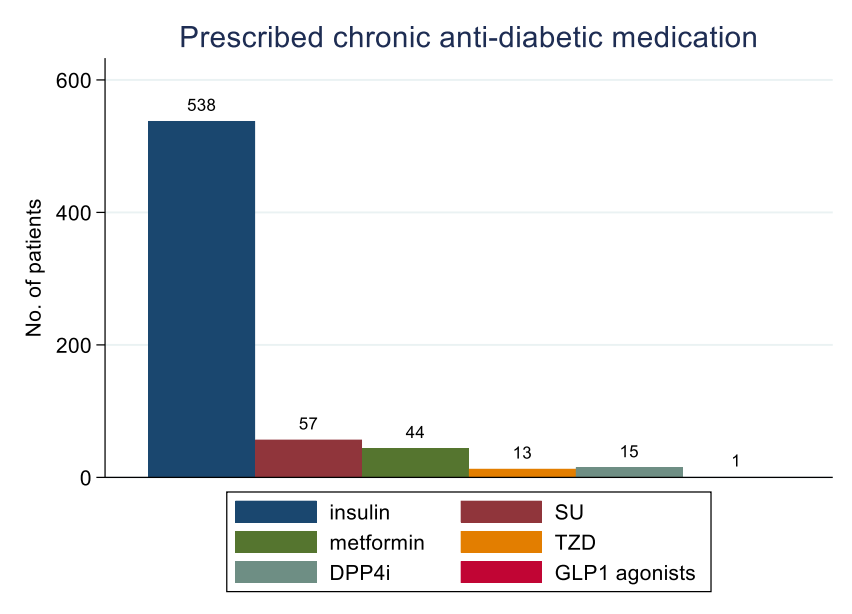
Predictors of hypoglycaemia	Number of studies
Pre-treatment blood glucose	13
Insulin dose	8
Kidney failure	5
Diabetes	4
Weight/Body mass index	2
Age	2
Male sex	1
Female sex	1
Emergency department treatment	2

All predictors included were statistically significant, $P<0.05$

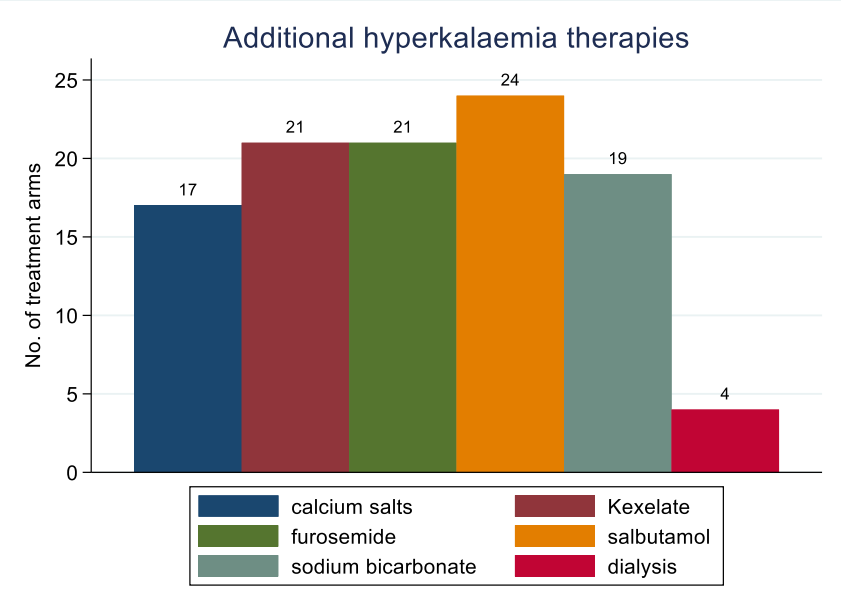
S1 Fig. Number of patients prescribed drugs associated with hyperkalaemia



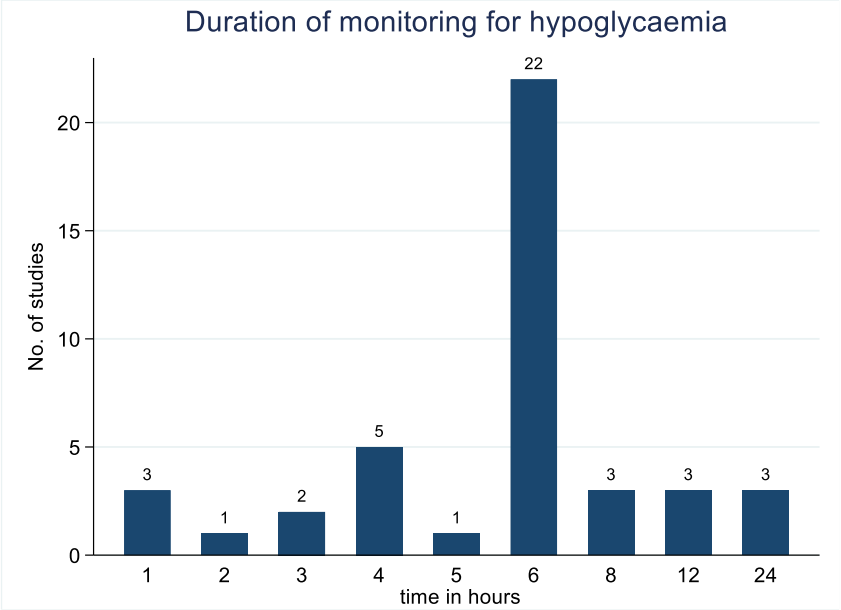
S2 Fig. Number of patients prescribed chronic anti-diabetic medication



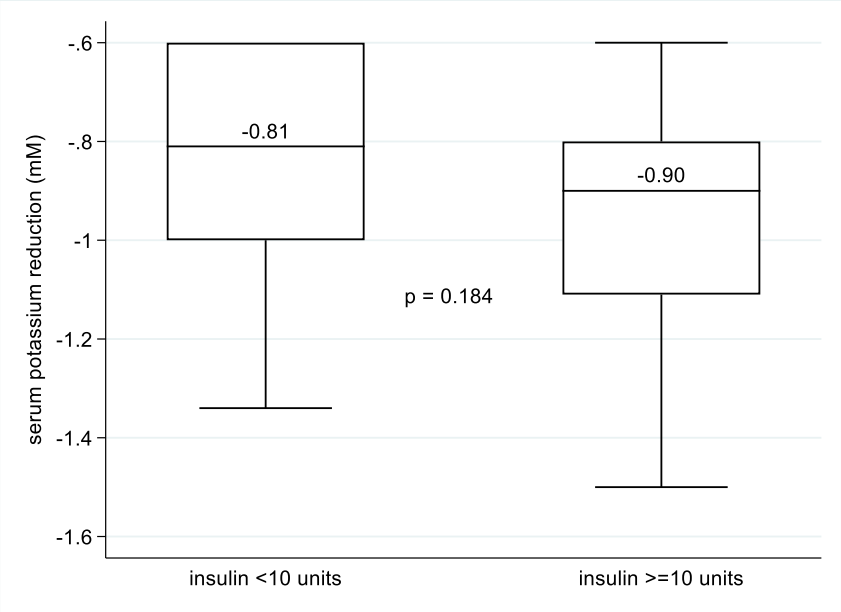
S3 Fig. Number of studies reporting additional hyperkalaemia therapies



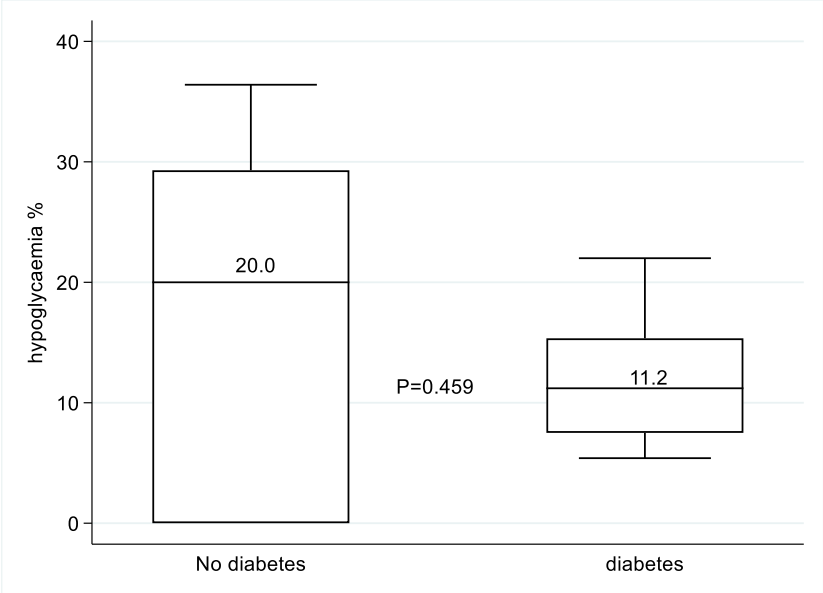
S4 Fig. Duration of monitoring for hypoglycaemia



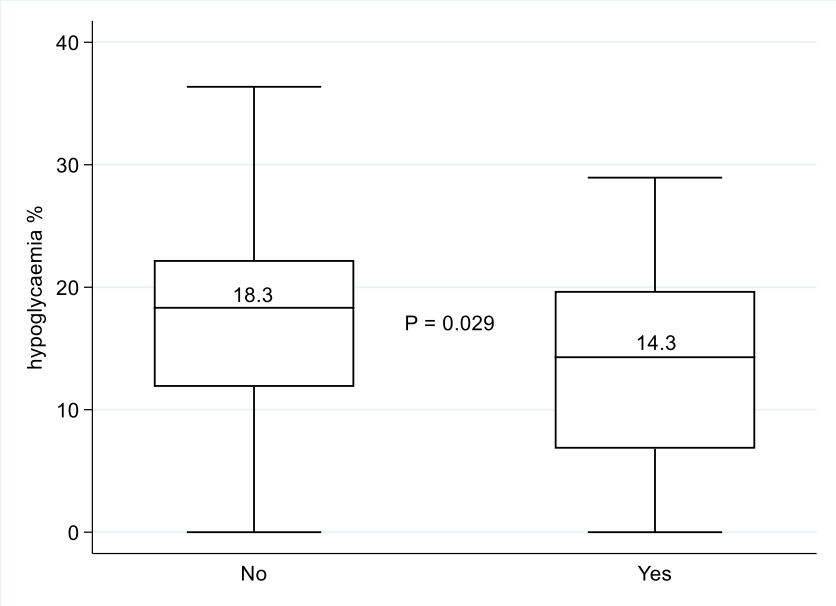
S5 Fig. Comparison of the average reduction in serum potassium concentration with <10 units vs. ≥10 units of insulin



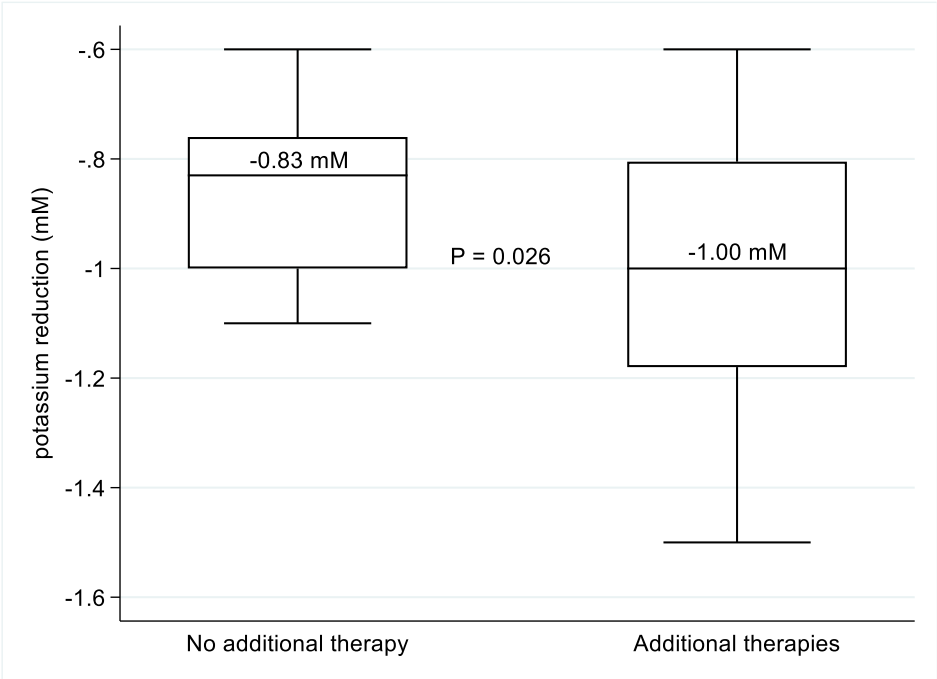
S6 Fig. Rates of hypoglycaemia by diabetic status



S7 Fig. Rates of hypoglycaemia by additional hyperkalaemia therapies



8 Fig. Average reduction in serum potassium concentration by additional hyperkalaemia therapies



CHAPTER 4

IDENTIFYING KNOWLEDGE GAPS AMONG MEDICAL STAFF

Knowledge of medical specialists on the emergency management of hyperkalaemia with a focus on insulin-based therapy

Published paper:

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Knowledge of medical specialists on the emergency management of hyperkalaemia with a focus on insulin-based therapy

AFRICAN ASSOCIATION OF NEPHROLOGY
Leading Nephrology in Africa

AJN

Method

Survey on REDCap

51 medical specialists

47% Nephrologists

53% Non-nephrologists

Results

	Initiate therapy at K of 6 mmol/L	Blood gas machine accurately measure K	ECG before starting treatment
Non-nephrologists	26%	14%	22%
	P < 0.01	P = 0.67	P = 0.02
Nephrologists	63%	11%	12%

22% Monitored the serum glucose concentration beyond 2 hours following insulin-based therapy

22% Thought that hypoglycaemia was an uncommon complication if dextrose also was administered

Conclusion: There is a need to address knowledge gaps, particularly around the optimal and safe use of insulin-based therapies. Our findings and recommendations should be useful in informing the development of consensus guidelines and educational resources on hyperkalaemia.

Mogamat-Yazied Chothia, Usuf Chikte, Mogamat Razeen Davids.
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ORIGINAL ARTICLE

Knowledge of medical specialists on the emergency management of hyperkalaemia with a focus on insulin-based therapy

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ABSTRACT

Introduction: Hyperkalaemia is a common electrolyte disorder in hospitalised patients and may cause life-threatening cardiac arrythmias and death. There is a lack of consensus regarding its optimal management, which may result in wide variations in practice and the guidance provided to junior staff.

Methods: We conducted a survey on a Research Electronic Data Capture (REDCap) platform to evaluate the knowledge of medical specialists regarding the diagnosis and management of hyperkalaemia, with a focus on insulin-based therapy. A convenience sample of 70 specialists in nephrology, internal medicine, emergency medicine and critical-care medicine were invited to participate. Comparisons were also made between nephrologists and non-nephrologists.

Results: A total of 51 medical specialists responded, of whom 47% were nephrologists. They were more likely to initiate therapy at a potassium concentration ([K]) of 6 mmol/L, whereas non-nephrologists tended to start at a lower concentration ($P < 0.01$). Half the respondents regarded blood gas machine measurements as providing an accurate measure of [K]. Non-nephrologists were more likely to perform an ECG before starting treatment ($P = 0.02$). All respondents regarded insulin and dextrose as the most effective and reliable means for shifting K. Only 22% monitored the serum glucose concentration beyond 2 hours following insulin-based therapy, and 22% thought that hypoglycaemia was an uncommon complication if dextrose also was administered.

Conclusions: This is the first comprehensive survey to report on the knowledge of specialists regarding the emergency management of hyperkalaemia. There is a need to address knowledge gaps, particularly around the optimal and safe use of insulin-based therapies. Our findings and recommendations should be useful in informing the development of consensus guidelines and educational resources on hyperkalaemia.

Keywords: hypoglycaemia; insulin; dextrose; glucose; electrocardiogram.

INTRODUCTION

Hyperkalaemia is a common electrolyte disorder encountered in hospitalised patients, with a reported incidence rate of 2.8 cases per 100 patient-years and a prevalence rate of 6.3% [1,2]. Since potassium (K) is responsible for maintaining the resting membrane potential of skeletal muscle cells and the conducting system of the heart, hyperkalaemia may result in respiratory muscle weakness, cardiac arrhythmias, and death [3].

Principles of management include protecting the heart using calcium salts, shifting K intracellularly using insulin and dextrose, beta-2 agonist nebulisations and sodium bicarbonate when hyperkalaemia is accompanied by acidosis, eliminating K from the body via the kidneys and gastrointestinal tract, and reducing sources of K and stopping drugs that interfere with the renal elimination of potassium.

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Insulin-based therapy is the most favoured pharmacological method for treating hyperkalaemia [4-6], although few randomised controlled trials have been performed [7,8]. Dextrose is usually co-administered to prevent hypoglycaemia. Various recommendations exist regarding the dosing, sequence and rates of administration for insulin and dextrose [5,9]. As a result, there are wide variations in practice [10]. Hypoglycaemia, a serious complication of insulin-based therapy, has been reported to occur in as many as 75% of patients [5]. Factors that may influence the risk of this complication include the dose of insulin administered [11], the dose of dextrose [12], the baseline serum glucose concentration [12-15] and the presence of kidney failure [11].

There is a paucity of data on the knowledge and practice patterns of doctors regarding the emergency management of hyperkalaemia. A survey that assessed the knowledge of trainees reported a low overall score of 52% [16]. The lowest scores were achieved for knowledge regarding the normal [K] range, the threshold for treating hyperkalaemia and drugs that may result in hyperkalaemia. Another survey of paediatricians regarding the choice and sequence of administration of drugs during cardiac arrest associated with hyperkalaemia reported significant variability and recommended that a standardised approach be developed to improve management [17]. Lastly, a survey of the practice patterns of residents and specialists regarding the treatment of hyperkalaemia in the emergency department reported wide variation in practice. The authors speculated that this may have resulted from concerns regarding the risk of hypoglycaemia when insulin-based therapy was used in patients with kidney failure [10].

In summary, since there is a lack of consensus and a paucity of data regarding the knowledge of medical specialists on the emergency management of hyperkalaemia and many medical specialists are involved in training medical students and junior colleagues, we conducted this survey to identify their current knowledge and practice patterns, with a focus on insulin-based therapy. The aim was to identify knowledge gaps and to inform the development of learning resources to guide the optimal management of this life-threatening condition.

METHODS

We performed a survey on a convenience sample of medical specialists who frequently encounter patients with hyperkalaemia in their clinical practice. Participants were asked to complete the survey according to their current practice.

Items that were included in the survey (Tables 1 and 2, supplementary Tables S1, S2 and S3) were selected based on published guidelines [18-20], protocols in major textbooks [21-23] and also drew on our own experience. They focused on the following aspects: diagnostic tests which would guide treatment such as blood tests and the electrocardiogram (ECG), pharmacological and non-pharmacological therapies with a focus on insulin-based therapies, and the treatment-related adverse event of hypoglycaemia (Tables 1 and 2).

Survey items on diagnostic tests included the potassium concentration ([K]) that should trigger therapy, and the utility of the ECG and point-of-care potassium measurements.

Items on pharmacological management included protecting the heart using calcium salts, shifting K into cells using insulin-based therapy, eliminating potassium from the body, and removing sources of potassium intake and stopping drugs that interfere with renal potassium excretion.

In relation to insulin, the survey items tested knowledge of the type of insulin to be used, and the doses and rates of administration. This included the time required for the [K] to reach its nadir, the expected magnitude of the drop, whether [K] was expected to return to pre-shift concentrations, and the definition of refractory hyperkalaemia.

Regarding treatment-related adverse events, we included items on the anticipation of hypoglycaemia when shifting potassium with insulin, monitoring of blood glucose concentrations, and the dose, route, and timing of dextrose administration.

The survey was developed and managed using the Research Electronic Data Capture (REDCap) platform [24]. After distribution, email reminders were sent weekly until a threshold response rate of at least 60% was achieved. Permission to conduct this study was granted by the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC study number: 10988).

Data analysis

Data were exported from REDCap into Stata version 16.1 (StataCorp LLC, Texas, USA) and summarised using counts and percentages. Chi-squared or Fisher's exact tests were used to compare choices between nephrologists and other specialists. Statistical significance was regarded as a P value of less than 0.05 and 95% confidence intervals were used.

RESULTS

A total of 51 of 70 specialists responded, a rate of 73%. Of these, 24 (47%) were nephrologists and the remainder were specialist physicians (18, 35%), emergency medicine physicians (7, 14%) and intensivists (2, 4%).

[K] prompting therapy and diagnostic tests (Table 1 and Table S1)

Nearly half the respondents (43%) selected a [K] of 6 mmol/L as the threshold value that would prompt their treatment of hyperkalaemia; 63% of the nephrologists selected 6 mmol/L as compared with only 26% of the non-nephrologists ($P < 0.01$) (Figure 1).

Most respondents (96%) regarded laboratory K measurements as accurate whereas only half considered point-of-care measurements on blood gas samples as accurate.

Two-thirds of respondents routinely performed an ECG before deciding whether a patient required treatment for hyperkalaemia, with more non-nephrologists performing an ECG ($P = 0.02$). Nearly three quarters of respondents thought that there was poor correlation between [K] and the presence of ECG changes. The ECG change that would most frequently prompt the initiation of treatment was tall, tented T waves (94%), whereas broad QRS complexes, ventricular tachycardia/fibrillation, flattened or absent P waves, sine waves and sinus bradycardia were selected by 86%, 77%, 77%, 71% and 57% of respondents, respectively.

Pharmacological management of hyperkalaemia (Table 2 and Table S2)

Most of the respondents indicated that they would invariably administer calcium salts. Of those who reported that they would not use calcium salts routinely, 24% commented that they would use them only when hyperkalaemia was associated with ECG changes.

Regarding therapies used during the emergency treatment, the two most frequently employed therapies were insulin and dextrose (100%) and calcium salts (96%). All respondents selected insulin and dextrose as the most effective and reliable means for shifting K into cells and used short-acting insulin. Nearly three quarters used a dose of 10 units of insulin. Insulin was administered as a push (bolus) by half, whereas a quarter administered it over 30 minutes. Less than half expected the [K] value to reach its nadir at 60 minutes. Most (63%) expected an average decrease in the serum [K] of 1 mmol/L. Most (61%) anticipated serum [K] to return to its pre-shift value and expected it to occur at 2–3 hours following treatment with insulin (63%). Just over half defined refractory hyperkalaemia as two or more shifts

Table 1. Potassium concentration prompting therapy, and diagnostic tests.

	All (n = 51)	Other (n = 27)	Nephrologist (n = 24)	P value
	Diagnostic			
Serum [K] prompting treatment (mmol/L)				
>5.0	1 (2)†	1 (4)	0 (0)	<0.01
>5.5	13 (26)	12 (44)	1 (4)	
>6.0*	22 (43)	7 (26)	15 (63)	
>6.5	13 (26)	5 (19)	8 (33)	
>7.0	2 (4)	2 (7)	0 (0)	
Accurate method of measurement (select all that apply)				
Blood gas	25 (49)	14 (53)	11 (46)	0.67
Laboratory*	49 (96)	26 (96)	23 (96)	1.00
Routine ECG?				
Yes*	34 (67)	22 (82)	12 (50)	0.02
No	17 (33)	5 (19)	12 (50)	
Correlation between serum [K] and the ECG				
Yes	11 (22)	6 (22)	5 (21)	0.86
No*	38 (75)	21 (78)	17 (71)	
Not sure	1 (2)	0 (0)	1 (4)	
ECG changes prompting treatment (select all that apply)				
Sinus bradycardia*	29 (57)	14 (52)	15 (63)	0.44
Flattened or absent P waves*	39 (77)	21 (78)	18 (75)	0.81
Broad QRS complexes*	44 (86)	24 (89)	20 (83)	0.69
Tall, tented T waves	48 (94)	26 (96)	22 (92)	0.59
Sine waves*	36 (71)	18 (67)	18 (75)	0.51
Ventricular tachycardia/fibrillation*	39 (77)	19 (70)	20 (83)	0.28

Abbreviation: ECG, electrocardiogram. [K], potassium concentration. *Preferred or correct option(s). †Percentage in brackets.

required within 24 hours. Most (94%) had safety concerns when using insulin therapy, mainly related to the risk of hypoglycaemia.

Nearly all respondents (82%) routinely checked blood glucose concentration before administering insulin treatment. Most used 50 mL (57%) or 100 mL (41%) of 50% dextrose. Approximately half administered the dextrose mixed with insulin whereas the remainder provided it before (37%) or after (11%) insulin administration. Nearly all (96%) administered this treatment via the intravenous route. One third expected hypoglycaemia to occur within one hour following the administration of insulin and dextrose, another third expected hypoglycaemia after 1–2 hours, and 22% thought that hypoglycaemia was uncommon if dextrose was administered. Two-thirds checked the blood glucose concentration before insulin administration whereas only 22% checked it at 3 hours after insulin administration (Figure 2).

K elimination

Although 80% of the study population used drugs to eliminate K from the body, nearly all the nephrologists made use of this treatment (96% vs. 67%, $P < 0.01$). Drug classes used included K-binding resins (85%), loop diuretics (76%), cathartics (42%) and intravenous sodium bicarbonate (42%). Most of the respondents (88%) were aware of serious gastrointestinal adverse effects, particularly colonic ulceration/colitis, colonic necrosis, and bowel obstruction associated with the use of K-binding resin.

Non-pharmacological management (Table S3)

Nearly all respondents routinely stopped foods with a high potassium content (88%) and drugs that interfere with the renal elimination of K (96%).

DISCUSSION

We identified important shortcomings regarding the knowledge and management of hyperkalaemia among medical specialists. These included tented T waves as the most common ECG change to trigger therapy, the time for [K] to reach its nadir following insulin administration, whether the potassium concentration would return to its pre-shift value and when this was expected to occur, defining refractory hyperkalaemia, and the expectation and surveillance of hypoglycaemia following insulin-based therapy.

On the other hand, most of the respondents were aware that the ECG correlated poorly with [K], that short-acting insulin and dextrose was the most reliable method for shifting K and that Kexelate use was associated with colonic/bowel necrosis.

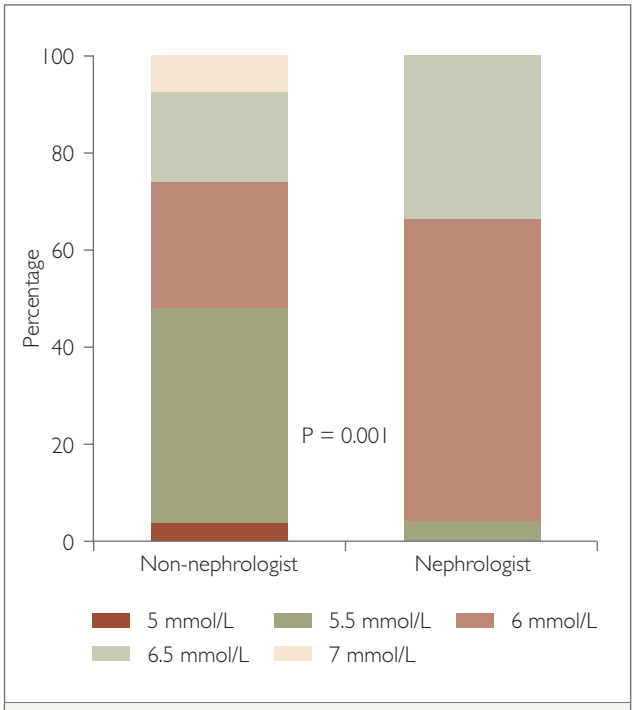

Figure 1. Threshold potassium concentrations prompting treatment of hyperkalaemia by nephrologists and non-nephrologists.

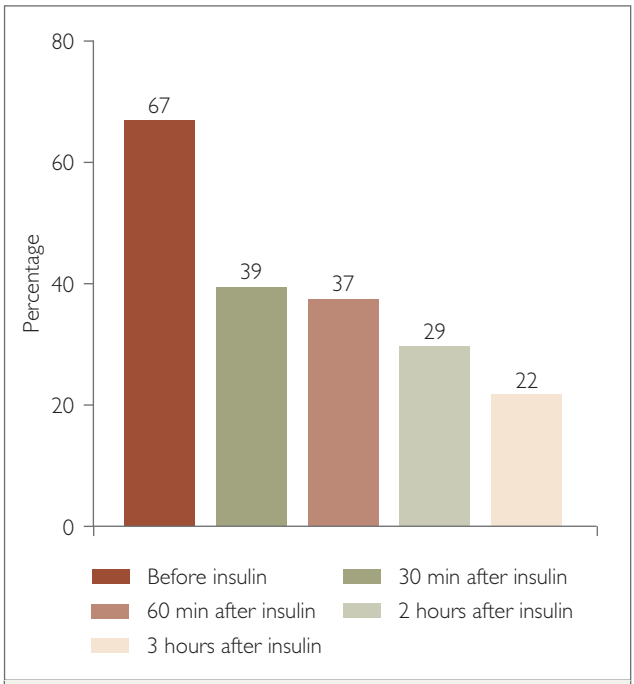

Figure 2. Proportion of medical specialists checking the capillary glucose concentrations before, as well as 30 minutes, 60 minutes, 2 hours and 3 hours after insulin administration.

Nephrologists tended to start therapy at a higher range of serum [K] (6.0–6.5 mmol/L), defined by many as moderate to severe hyperkalaemia [9,25]. We speculate that this is because of the high frequency with which they encounter patients with severe hyperkalaemia. A recent KDIGO con-

Table 2. Pharmacological management of hyperkalaemia.

	All (n = 51)	Other (n = 27)	Nephrologist (n = 24)	P value
K-lowering therapies				
Therapies frequently used				
Calcium salts	49 (96)†	26 (96)	23 (96)	1.00
Beta-2 agonist nebulisations	20 (39)	13 (48)	7 (29)	0.17
Intravenous sodium bicarbonate	18 (35)	8 (30)	10 (42)	0.37
Insulin and dextrose	51 (100)	27 (100)	24 (100)	-
Potassium-binding resins	28 (55)	13 (48)	15 (63)	0.30
Loop diuretics	18 (35)	8 (30)	10 (42)	0.37
Protect the heart				
Routine calcium salt administration				
Yes	36 (71)	18 (67)	18 (75)	0.51
No*	15 (29)	7 (33)	6 (25)	
Shift K into cells				
Most effective and reliable method for shifting potassium				
Intravenous insulin and dextrose*	51 (100)	27 (100)	24 (100)	-
Beta-2 agonist nebulisations	0 (0)	0 (0)	0 (0)	
Intravenous sodium bicarbonate	0 (0)	0 (0)	0 (0)	
Intravenous dextrose only	0 (0)	0 (0)	0 (0)	
Type of insulin used				
Short acting*	51 (100)	27 (100)	24 (100)	-
Intermediate acting	0 (0)	0 (0)	0 (0)	
Long acting	0 (0)	0 (0)	0 (0)	
Dose of insulin used (units)				
5	9 (18)	3 (11)	6 (25)	0.14
10*	38 (74)	22 (82)	16 (67)	
15	1 (2)	0 (0)	1 (4)	
20	2 (4)	2 (7)	0 (0)	
30	1 (2)	0 (0)	1 (4)	
Rate of insulin administration				
Push (Bolus)*	27 (53)	13 (48)	14 (58)	0.30
Over 5 min	7 (14)	4 (15)	3 (13)	
Over 30 min	13 (26)	6 (22)	7 (29)	
Over 1 h	4 (8)	4 (15)	0 (0)	
Over 2 h	0 (0)	0 (0)	0 (0)	
Expected time to reach its lowest concentration (min)				
15	10 (20)	6 (22)	4 (17)	0.20
30	10 (20)	6 (22)	4 (17)	
45	5 (10)	4 (15)	1 (4)	
60*	22 (43)	11 (41)	11 (46)	
120	4 (8)	0 (0)	4 (17)	
Expected average decrease in the serum potassium concentration (mmol/L)				
0.5	4 (8)	1 (4)	3 (13)	0.50
1.0*	32 (63)	17 (63)	15 (61)	
1.5	13 (26)	7 (26)	6 (25)	
2.0	2 (4)	2 (7)	0 (0)	
2.5	0 (0)	0 (0)	0 (0)	
Anticipation of serum [K] to return to its pre-shift value				
Yes*	31 (61)	15 (56)	16 (67)	0.61
No	13 (26)	7 (26)	6 (25)	
Unsure	7 (14)	5 (19)	2 (8)	
Timing of serum [K] to return to its pre-shift value (h)	N = 30	N = 14	N = 16	
2–3	19 (63)	7 (50)	12 (75)	0.26
4–6*	9 (30)	5 (36)	4 (25)	
≥7	2 (7)	2 (14)	0 (0)	

Table 2 continued. Pharmacological management of hyperkalaemia.

	All (n = 51)	Other (n = 27)	Nephrologist (n = 24)	P value
	Shift K into cells			
Defining refractory hyperkalaemia				
Serum K does not decrease after insulin therapy*	20 (39)	9 (33)	11 (46)	0.58
Two or more shifts required within 24 h	27 (53)	15 (56)	12 (50)	
Other	4 (8)	3 (11)	1 (4)	
Safety concerns when using insulin				
Yes*	48 (94)	25 (93)	23 (96)	1.00
No	3 (6)	2 (7)	1 (4)	
Checking blood glucose concentration before administering insulin				
Yes*	42 (82)	23 (85)	19 (79)	0.72
No	9	4 (15)	5 (21)	
Routine administration of dextrose?				
Yes*	46 (90)	23 (85)	23 (96)	0.35
No	5 (10)	4 (15)	1 (4)	
Volume of 50% dextrose administered when using insulin (mL)	N = 46	N = 23	N = 23	
50	26 (57)	13 (57)	13 (57)	1.00
100*	19 (41)	10 (44)	9 (39)	
200	0 (0)	0 (0)	0 (0)	
300	1 (2)	0 (0)	1 (4)	
Timing of dextrose administration	N = 46	N = 23	N = 23	
Before insulin*	17 (37)	8 (35)	9 (39)	0.29
Mixed with insulin	24 (52)	14 (61)	10 (44)	
After insulin	5 (11)	1 (4)	4 (17)	
Route of dextrose administration				
Oral	1 (2)	1 (4)	0 (0)	1.00
Intravenous*	49 (96)	26 (96)	23 (96)	
Timing of hypoglycaemia after insulin-based therapy				
0–1 h after	17 (33)	10 (37)	7 (29)	0.85
1–2 h after	16 (31)	9 (33)	7 (29)	
2–3 h after*	7 (15)	3 (11)	4 (17)	
Hypoglycaemia is uncommon if dextrose is given	11 (22)	5 (19)	6 (25)	
Checking blood glucose concentration relative to insulin (select all that apply)				
Before	34 (67)	18 (67)	16 (67)	1.00
5 min after	7 (14)	5 (19)	2 (8)	0.42
30 min after	20 (39)	8 (30)	12 (50)	0.14
60 min after	19 (37)	8 (30)	11 (46)	0.23
2 h after*	15 (29)	5 (19)	10 (42)	0.07
3 h after*	11 (22)	6 (22)	5 (21)	0.90
I do not check the glucose concentration	0 (0)	0 (0)	0 (0)	-
	K elimination			
Routine use of drugs to eliminate K?				
Yes	41 (80)	18 (67)	23 (96)	<0.01
No	10 (20)	9 (33)	1 (4)	
Drug(s) used to eliminate K (select all that apply)	N = 41	N = 18	N = 23	
K-binding resins (Kexelate)	35 (85)	16 (89)	19 (83)	0.13
Loop diuretics	31 (76)	17 (94)	14 (20)	0.73
Cathartics	17 (42)	9 (50)	8 (35)	1.00
Intravenous sodium bicarbonate	17 (42)	8 (44)	9 (39)	0.55
Aware of serious adverse effect(s) of Kexelate?				
Yes*	45 (88)	24 (89)	21 (88)	1.00

Abbreviation: [K], potassium concentration. *Preferred or correct option(s). †Percentage in brackets.

troversies paper supports the selection made by nephrologists along with the accompaniment of ECG changes [9]. However, their recommendation was based on the currently available studies of stable, pre-dialysis patients. Thus, the [K] value recommended to prompt the emergency treatment has not been tested in acute, unstable patients.

Only half of the respondents considered blood gas [K] measurements as accurate. Since there are often delays in reporting the laboratory [K] value and the diagnostic accuracy of the ECG is poor, the blood gas machine is an important point-of-care tool in the emergency department. A recent study that compared the difference in measurement between a blood gas machine and laboratory samples found that the average blood gas measurements were 0.4 mmol/L lower than laboratory values, with this negative bias remaining constant across the hyperkalaemic range [26]. The authors suggested that clinicians should consider using blood gas K measurements but should make the adjustment for the 0.4 mmol/L difference in concentrations.

Most non-nephrologists indicated that they routinely performed an ECG before deciding whether treatment was needed. There is a poor correlation between the ECG findings of hyperkalaemia and serum [K] [27] and this was acknowledged by most respondents. However, many guidelines recommend that an ECG be performed when hyperkalaemia is a consideration [9,18], since it is easily performed in the emergency department and there are often delays in the reporting of laboratory K measurements.

Most respondents were prompted to treat hyperkalaemia when accompanied by classic changes involving P waves and QRS complexes, and ventricular tachycardia/fibrillation. However, although tall, tented T waves are the first classic ECG change to appear during the evolution of hyperkalaemia, previous studies have not demonstrated any association with adverse outcomes [28]. On the other hand, sinus bradycardia was the least common ECG finding to prompt therapy despite its high prevalence in patients with hyperkalaemia [29] and its strong association with short-term adverse outcomes [28].

Regarding pharmacological therapy, all the respondents indicated that they regarded insulin and dextrose therapy as the most effective and reliable method for shifting K into cells. This was not surprising because insulin-based therapy is regarded by most authorities as the cornerstone of treatment [4]. However, several knowledge gaps of concern were identified. Fewer than half of the respondents were aware that serum [K] would reach its nadir at 60 minutes after insulin was administered [5,30] and less than two-thirds indicated that they anticipated the [K] value to return to its pre-shift value. Only a third expected this to occur at 4–6 hours following insulin therapy. This may explain why more than half the respondents regarded refractory hyperkalaemia as two or more shifts required within 24 hours. Since the intracellular shifting effect lasts only up to 6 hours, several shifts may be required within a 24-hour period. We recommend that the term "refractory hyperkalaemia" be used when serum [K] does not decrease following a single attempt using insulin.

Hypoglycaemia is the most common and serious complication of insulin-based therapy, occurring three to six hours following therapy [30]. Of concern was the low expectation of hypoglycaemia by respondents, with only 14% anticipating hypoglycaemia between 2–3 hours after insulin administration and 22% indicating that hypoglycaemia was uncommon if dextrose was co-administered. Only 30% checked serum glucose concentration at 2 hours, and only 22% at 3 hours. A systematic review of the management of hyperkalaemia reported that hypoglycaemia occurred in up to 75% of patients [5]. Most of these episodes occurred when 25 g of dextrose (50 mL of 50% dextrose) were used. Lower baseline serum glucose concentrations have been associated with a higher risk of hypoglycaemia following treatment with insulin [12-15,31]. We recommend that, in patients with a serum glucose concentration of less than 10 mmol/L, 50 g of dextrose (100 mL of 50% dextrose) be used, and that patient symptoms and serum glucose concentrations be monitored for at least three hours, and up to six hours, following insulin-based therapy.

Nearly all nephrologists indicated that they routinely used drugs to eliminate K. Some of these therapies, such as K-binding resins, are of questionable efficacy during the emergency treatment [32]. We speculate that because nephrologists were more likely to be involved in the chronic care of patients prone to develop hyperkalaemia, they are more likely to prescribe therapies that would reduce total body K.

Based on the knowledge gaps identified and the appraisal of the current literature, we recommend the following:

1. A [K] ≥ 6 mmol/L should prompt the start of therapy, or any degree of hyperkalaemia which is accompanied by symptoms or ECG changes.
2. Point-of-care blood gas [K] measurements may be used in the emergency setting provided adjustment for the 0.4 mmol/L negative bias is made.
3. An ECG should be performed on all patients.
4. Calcium salts should be administered only when there are ECG changes.

5. All ECG changes, except tented T waves, should trigger therapy. This includes sinus bradycardia.
6. Short-acting insulin should be administered as a push (bolus) of 10 units, intravenously. Lower doses (5 units) should be considered in patients with chronic kidney disease and kidney failure [33].
7. In patients with a serum glucose concentration <10 mmol/L, 50 g of dextrose (100 mL of 50% dextrose) should be infused, before administering insulin.
8. Patients should be monitored for symptoms of hypoglycaemia and serum glucose concentrations measured hourly for at least three hours, and up to six hours, following insulin-based therapy.
9. The [K] should be checked one hour following insulin-based therapy as this is when the nadir is expected.
10. The term "refractory hyperkalaemia" should be used when serum [K] does not decrease at the one-hour time point following a single attempt using insulin-based therapy.

CONCLUSIONS

This is the first comprehensive survey to report on the knowledge of specialists regarding the emergency management of hyperkalaemia. There is a need to address knowledge gaps, particularly around the optimal and safe use of insulin-based therapies. Our findings and recommendations should be useful in informing the development of consensus guidelines and educational resources on hyperkalaemia.

Supplementary materials

Questions from the REDCap survey are provided as Tables S1, S2 and S3 in Appendix 1.

Conflicts of interest

No conflicts of interest to declare.

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9. The [K] should be checked one hour following insulin-based therapy as this is when the nadir is expected.
10. The term "refractory hyperkalaemia" should be used when serum [K] does not decrease at the one-hour time point following a single attempt using insulin-based therapy.

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APPENDIX 1: SUPPLEMENTARY TABLES

Table S1. Potassium concentration prompting therapy, and diagnostic tests.

Which serum potassium concentration would prompt your initiation of the emergency treatment for hyperkalaemia?
>5.0 mmol/L
>5.5 mmol/L
>6.0 mmol/L
>6.5 mmol/L
>7.0 mmol/L
Which method do you consider an accurate measure of the potassium concentration? (Select all that apply)
Blood gas – Yes/No
Laboratory – Yes/No
Is it your current practice to routinely do an electrocardiogram (ECG) before deciding if your patient requires treatment for hyperkalaemia?
Yes
No
Is there a good correlation between the serum potassium concentration and the presence of ECG changes during hyperkalaemia?
Yes
No
Not sure
Which ECG change would prompt your initiation of treatment for hyperkalaemia? (Select all that apply)
Sinus bradycardia
Flattened or absent P waves
Broad QRS complex
Tall, tented T waves
Sine waves
Ventricular tachycardia/fibrillation

Abbreviation: ECG, electrocardiogram; K+, potassium.

Table S2. Pharmacological management of hyperkalaemia.

Do you always administer calcium salts (e.g., calcium gluconate) to patients with hyperkalaemia?
- Yes
- No

Which pharmacological therapies do you frequently use during the emergency treatment of hyperkalaemia?
- Calcium salts
- Beta-2 agonist nebulisations
- Intravenous sodium bicarbonate
- Insulin and glucose
- Potassium-binding resins
- Loop diuretics

What do you consider to be the most effective and reliable method for shifting potassium into cells during hyperkalaemia?
- Insulin and glucose
- Beta-2 agonist nebulisations
- Intravenous sodium bicarbonate
- Intravenous glucose only

When using insulin to shift potassium into cells, which type do you use?
- Short acting
- Intermediate acting
- Long acting

When using insulin to shift potassium into cells, what dose do you routinely administer?
- 5 units
- 10 units
- 15 units
- 20 units
- 30 units

At what rate do you usually administer the insulin?
- Push (Bolus)
- Over 5 min
- Over 30 min
- Over 1 hour
- Over 2 hours

How long after administering insulin therapy do you expect the serum potassium to reach its lowest concentration?
- 15 min
- 30 min
- 45 min
- 60 min
- 120 min

What do you think is the average decrease in the serum potassium concentration during the peak effect of insulin therapy?
- 0.5 mmol/L
- 1.0 mmol/L
- 1.5 mmol/L
- 2.0 mmol/L
- 2.5 mmol/L

Do you anticipate the serum potassium concentration to return to its pre-shift value?
- Yes
- No
- Not sure

When do expect the serum potassium concentration to return to its pre-shift concentration following treatment with insulin?
- 2-3 hours
- 4-6 hours
- ≥ 7 hours

What do you regard as refractory hyperkalaemia?
- Serum K does not decrease after insulin therapy
- Two or more shifts required within 24-hrs
- Other

Do you have any safety concerns when using insulin to treat hyperkalaemia?
- Yes
- No

Do you routinely check the blood glucose concentration before administering insulin for the treatment of hyperkalaemia?
- Yes
- No

Before administering insulin for the treatment of hyperkalaemia, do you routinely administer glucose?
- Yes
- No

How much glucose do you usually administer when using insulin?
- 50 mL of 50% dextrose
- 100 mL of 50% dextrose
- 200 mL of 50% dextrose
- 300 mL of 50% dextrose

When do you administer the glucose in relation to insulin therapy?
- Before the insulin
- Mixed with insulin
- After insulin

How do you administer the glucose?
- Oral
- Intravenous

When do you expect hypoglycaemia after the administration of insulin and glucose for the treatment of hyperkalaemia?
- 0-1 hour after
- 1-2 hours after
- 2-3 hours after
- Hypoglycaemia is uncommon if glucose is given

When do you check the blood glucose concentration relative to insulin administration? (Select all that apply)
- Before
- 5 minutes after
- 30 minutes after
- 60 minutes after
- 2 hours after
- 3 hours after
- I do not check the glucose concentration

Do you routinely use drugs to increase the elimination of potassium during your management of hyperkalaemia?
- Yes
- No

Which drug(s) do you use to increase the elimination of potassium? (Select all that apply)
- K-binding resins (Kexelate)
- Loop diuretics
- Cathartics
- Intravenous sodium bicarbonate

Are you aware of any serious adverse effect(s) of Kexelate?
- Yes
- No

Table S3. Non-pharmacological management of hyperkalaemia.

Do you routinely stop foods with high potassium content?
Yes
No
Do you routinely stop drugs that may interfere with the renal elimination of potassium?
Yes
No

CHAPTER 5

IMPROVING DIAGNOSTIC OPTIONS

A method comparison study of a point-of-care blood gas analyser with a laboratory auto-analyser for the determination of potassium concentrations during hyperkalaemia in patients with kidney disease

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A method comparison study of a point-of-care blood gas analyser with a laboratory auto-analyser for the determination of potassium concentrations during hyperkalaemia in patients with kidney disease

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Abstract

Introduction: Hyperkalaemia is a common electrolyte disorder that may cause life-threatening cardiac arrythmias. We aimed to determine the agreement of potassium concentrations between GEM premier 3500 point-of-care blood gas analyser (POC-BGA) and Roche Cobas 6000 c501 auto-analyser in patients with hyperkalaemia.

Methods: A prospective, cross-sectional study of all consecutive adult patients referred to the Renal Unit with a serum potassium concentration ≥ 5.5 mmol/L was performed. A total of 59 paired venous blood samples were included in the final statistical analysis. Passing-Bablok regression and Bland Altman analysis were used to compare the two methods.

Results: The median laboratory auto-analyser potassium concentration was 6.1 (5.9-7.1) mmol/L as compared to the POC-BGA potassium concentration of 5.7 (5.5-6.8) mmol/L with a mean difference of - 0.43 mmol/L and 95% upper and lower limits of agreement of 0.35 mmol/L and - 1.21 mmol/L, respectively. Regression analysis revealed proportional systematic error. Test for linearity did not indicate significant deviation (P = 0.297).

Conclusion: Although regression analysis indicated proportional systematic error, on Bland Altman analysis, the mean difference appeared to remain relatively constant across the potassium range that was evaluated. Therefore, in patients presenting to the emergency department with a clinical suspicion of hyperkalaemia, POC-BGA potassium concentrations may be considered a surrogate for laboratory auto-analyser measurements once clinicians have been cautioned about this difference.

Keywords: point-of-care; emergency department; potassium concentrations; hyperkalaemia

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Introduction

Potassium is the most abundant cation in the human body and is predominantly confined to the intracellular fluid compartment (ICF) (1). Most of the total body potassium (98%) is located within the ICF compartment. This distribution of potassium is the major determinant of the resting membrane potential of cells required for nerve excitation and muscle contraction. Potassium disorders may result in serious cardiac arrhythmias and/or muscle weakness (2).

Hyperkalaemia is a very common electrolyte disorder in hospitalised patients (3-5). The most common risk factors associated with hyperkalaemia include acute and chronic kidney disease, diabetes mellitus, cardiac failure, and drugs that interfere with the renin-angiotensin-aldosterone system (4,6). As the symptoms and physical findings of hyperkalaemia may be very subtle and nonspecific, the diagnosis of hyperkalaemia must be made by

alternative means. Since hyperkalaemia affects cardiac conduction, the electrocardiogram (ECG) is frequently used to identify patients at imminent risk for arrhythmias. This investigation is non-invasive, readily available, and easily performed in the emergency department. Numerous studies have reported that the ECG has poor diagnostic accuracy, regardless of the degree of hyperkalaemia (7,8). Therefore, direct measurements are required to accurately determine blood potassium concentration.

Two types of blood tests are possible. Serum or plasma potassium concentration can be measured in the laboratory, or whole blood potassium concentration can be determined by point-of-care blood gas analysers (POC-BGA). There may be a delay in the processing of the laboratory samples which may cause a factitious increased potassium concentration as well as delaying the initiation of therapy and therefore POC-BGA is an attractive alternative. It has been recommended that the potassium concentrations on POC-BGA can be reliably used in the emergency department (9).

Prompt access to results is crucial in the management of patients with life-threatening but reversible medical conditions such as hyperkalaemia. The reliance on point-of-care devices for clinical decision-making, particularly in the emergency setting, has gained much popularity due to its ease of use, less reliance on technical staff members, and most importantly, a marked reduction in turnaround time (TAT) (10,11).

Pseudohyperkalaemia is defined as a difference between serum and plasma potassium concentration of greater than 0.3 to 0.4 mmol/L provided that the sample was collected using the correct phlebotomy technique, remained at room temperature, and was analysed within one hour of sample collection. It is frequently encountered during thrombocytosis due to potassium release from platelets during clotting (12). Other causes include haemolysis, leukocytosis, pre-analytical errors such as potassium-ethylenediaminetetraacetic acid (K-EDTA) contamination, and other incorrect phlebotomy techniques such as fist clenching, prolonged tourniquet application, as well as delays in sample transport to the laboratory (13).

Few relevant studies have reported on the diagnostic accuracy of POC-BGA potassium concentration measurements relative to laboratory measurements, however, the average potassium concentrations reported in these studies were not in the hyperkalaemic range (14-17). We could only identify two retrospective studies that were performed in patients with hyperkalaemia (9,18). In view of the conflicting results from previous retrospective studies, we performed a prospective cross-sectional study of patients with hyperkalaemia with the aim to determine the agreement between GEM Premier 3500 (Instrumentation Laboratory, Massachusetts, United States of America) POC-BGA and Roche Cobas 6000 c501 (Roche Diagnostics GmbH, Mannheim, Germany) analyser potassium concentrations.

Materials and methods

Subjects

A cross-sectional study was conducted at Tygerberg Hospital, a 1380 bed tertiary care teaching hospital affiliated to the Faculty of Medicine and Health Sciences of Stellenbosch University. Adult patients (age > 18 years) referred to the Renal Unit with acute kidney injury or chronic kidney disease with hyperkalaemia (≥ 5.5 mmol/L) were included. To reduce the effect of pseudohyperkalaemia, all participants with leukocyte counts > 100 $x10^9$/L, platelet counts > 500 $x10^9$/L, and haemolysis were excluded, as shown in Figure 1.

Informed consent was obtained. Patients were referred based on prior laboratory auto-analyser measurements. This study was approved by the Human Research Ethics Committee of Stellenbosch University (study number: 7082) and performed according to the Declaration of Helsinki.

Methods

Paired venous blood samples were obtained from participants over a 6-week period from October to November 2018. Phlebotomy was performed by the same individual using the Joint European Federation of Clinical Chemistry and Laboratory Medi-

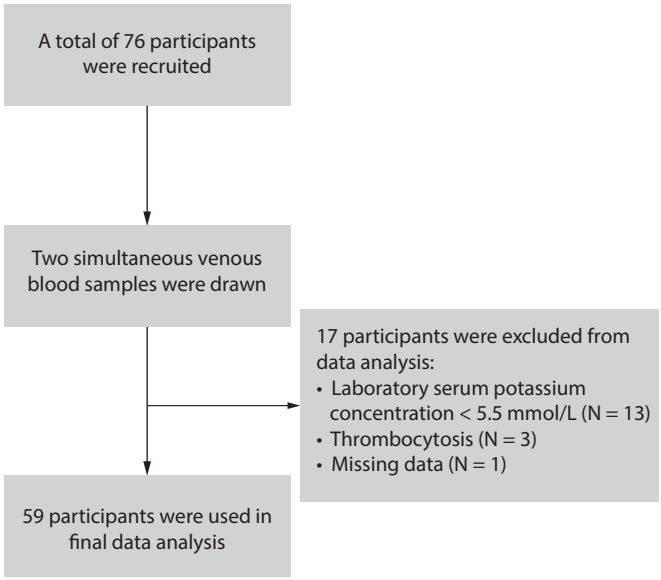

Figure 1. Consort diagram

cine (EFLM) and the Latin America Confederation of Clinical Biochemistry (COLABIOCLI) recommendations for venous blood sampling (19). Paired venous blood samples were drawn simultaneously from the brachial vein and a vein on the dorsum of the hand of the same upper limb because the contralateral upper limb was frequently cannulated with the infusion of intravenous fluids.

For the POC-BGA sample, 2.5 mL of venous blood was drawn with a 23-gauge, 0.65 mm butterfly needle into a prefilled, spray-dried calcium-balanced heparin syringe BD A-line syringe (Becton Dickinson, Wokingham, United Kingdom), capped and turned around gently for one mixing cycle. POC-BGA was performed within five minutes using the GEM Premier 3500 system (Instrumentation Laboratory, Massachusetts, United States of America).

For the laboratory analysis, a sample of 2.5 mL of venous blood was obtained using a closed-loop-system with the help of a vacutainer and bulldog needle into a serum separation tube (BD Vacutainer, Becton Dickinson, Wokingham, United Kingdom). The sample was mixed in the tube by gently inverting the tube for one mixing cycle. The samples were made to stand for at least 30 minutes at room temperature to allow it to clot and thereafter it was centrifuged for 10 minutes at a speed of 3000 revolutions *per* minute. The time of sample collection and time to centrifugation was noted. Samples were hand delivered to a designated laboratory technologist at the chemical pathology laboratory immediately following centrifugation.

The GEM Premier 3500 system (Instrumentation Laboratory, Massachusetts, United States of America) determines the potassium concentration using a potentiometric direct ion selective electrode (ISE). It does not subscribe to an external quality assurance (EQA) program, instead it uses Intelligent Quality Management (iQM). This internal quality assurance system provides continuous monitoring of the analytical process with real-time, automatic error detection. A specific ampoule calibrates the machine for high potassium concentrations (range: 6.2-6.8 mmol/L). During the study period, the measured analytical imprecision was 1% at a nominal target value of 6.8 mmol/L.

In the laboratory, the potassium concentration and the haemolysis index were measured using the Roche Cobas 6000 c501 system (Roche Diagnostics GmbH, Mannheim, Germany). Serum potassium concentration is measured using an indirect ISE method. For a potassium concentration of 6.44 mmol/L, the within-assay coefficient of variation (CV) was 0.5% and the within-laboratory CV was 0.7%. These were within the manufacturer's recommendation of 0.6% and 0.7%, respectively. Leukocyte and platelet counts were measured using the Siemens ADVIA 2120i haematology system (Siemens Healthcare GmbH, Erlangen, Germany).

The total allowable error (TEa) used for serum potassium was 5.6%, as specified in the Westgard Biological Variation Database (20).

Statistical analysis

Data were analysed using StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. The Shapiro-Wilks test was used to test for data normality. Data were expressed as median and interquartile range. Bland Altman analysis and Passing Bablok regression were used to assess the agreement between the two measurement methods. The 95% upper and

lower limits of agreement and mean difference was reported for the Bland Altman analysis and the 95% confidence interval (95%CI) for the intercept and the slope were reported for the Passing Bablok regression line. The cumulative sum test (cusum test) was used to calculate linearity between the two methods.

Results

Seventy-six patients were referred with hyperkalaemia of which 59 were included in the final statistical analysis. Seventeen patients were excluded from the final statistical analysis because the laboratory potassium concentration was < 5.5 mmol/L (N = 13), had thrombocytosis (N = 3), and missing data (N = 1).

The median age was 40 (32-47) years. Thirty participants were female. All participants had kidney disease with 38 having acute kidney injury and 21 with chronic kidney disease.

The median time from sample collection to completion of centrifugation of laboratory samples was 33 (30-36) minutes. The median laboratory potassium concentration was 6.1 (5.9-7.1) mmol/L as compared to the POC-BGA potassium concentration of 5.7 (5.5-6.8) mmol/L with a mean difference of -0.4 mmol/L.

Figure 2 shows the Passing Bablok regression line with associated 95%CI for the intercept and the slope. The mean difference was - 0.43 mmol/L. The Bland Altman analysis shows the mean difference with the associated 95% upper and lower limits of agreement for the two methods (Figure 3).

Discussion

To the best of our knowledge, this was the first prospective study to determine the agreement between POC-BGA and laboratory auto-analyser potassium concentrations in patients with hyperkalaemia and kidney disease. A difference in measurements was identified between GEM Premier 3500 POC-BGA and Roche Cobas 6000 c501 auto-analyser and most of the potassium values for the POC-BGA were outside of the TEa of 5.6%. With

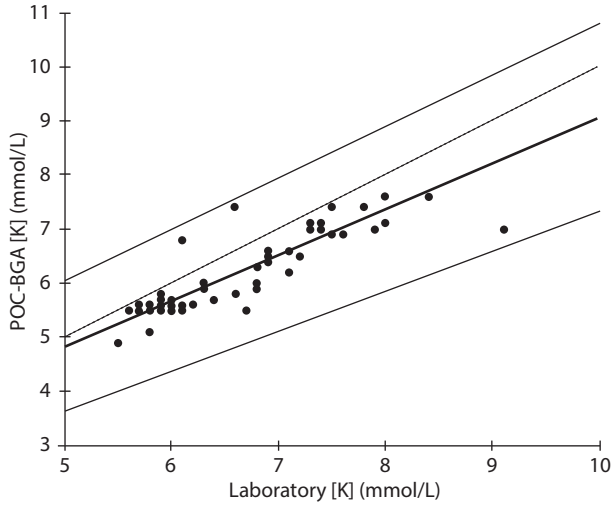

Figure 2. Passing Bablok regression of the two methods for hyperkalaemia. Scatter diagram with regression line and confidence intervals for regression line. Cusum test for linearity did not indicate significant deviation (P = 0.297). Gray lines represent 95% confidence intervals, black line represents the regression line (equation: y = 0.59 + 0.846x, 95%CI for the intercept was -0.09 to 1.26 and for the slope the 95% CI was 0.74 to 0.96) and dotted line represents the line of equality. POC-BGA – point-of-care blood gas analyser. [K] – potassium concentration.

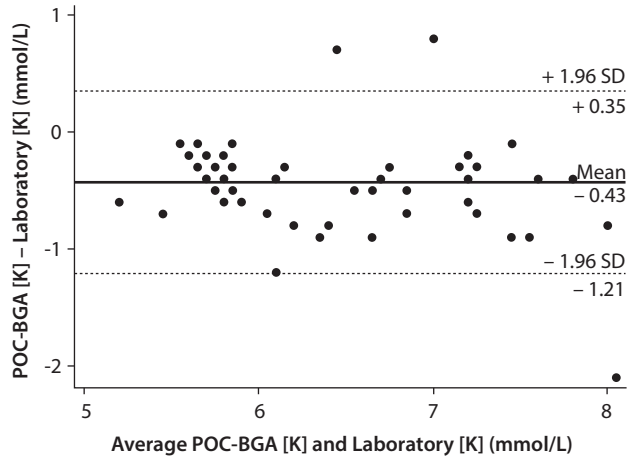

Figure 3. The Bland Altman analysis. Dashed lines indicate upper and lower limits of agreement and solid line indicates the mean difference. [K] – potassium concentration. POC-BGA – point-of-care blood gas analyser. SD – standard deviation.

the visual inspection of the Bland Altman analysis, the mean difference remained relatively constant across the full range of potassium concentrations. However, Passing Bablok regression analysis did not support a constant systematic error between the two methods since the 95%CI for the intercept did not differ significantly from 0; however, the 95%CI for the slope differed significantly from 1, indicating the presence of proportional systematic error (21). Although regression analysis indicated proportional error as the potassium concentration rose, we limited our samples to only include potassium concentrations of more than or equal to 5.5 mmol/L. This may have been diminished or absent if the full range of potassium concentrations were evaluated. Previous studies that included samples across a wider range of potassium concentrations did not report any proportional systematic error (22-24).

Few studies have reported on the agreement between the two methods. A study that examined the agreement between the two methods in patients with chronic kidney disease, reported a difference of -0.4 mmol/L (16). Although the latter study had a larger sample size, the median potassium concentrations were < 5.0 mmol/L. Despite this, the reported total error was within the recommended TEa at a threshold value of 5.5 mmol/L. Another study that compared the agreement of numerous analytes, including potassium concentration in critically ill patients, reported a difference of only 0.20 mmol/L, with most of the potassium values within the normal range. Gupta *et al.* compared 112 paired arterial blood gas samples with serum laboratory samples and reported a difference for potassium concentration of -0.14 mmol/L (25). The mean serum potassium concentration was within the normal range. In the latter study, after grouping serum potassium concentrations into < 3.5 mmol/L, 3.5 to 5.2 mmol/L and > 5.2 mmol/L, the associated differences were 0.07 mmol/L, 0.26 mmol/L and 0.28 mmol/L, respectively. The only other study to exclusively examine the agreement between the two methods with serum potassium concentrations of more than or equal to 6.0 mmol/L, reported a high mean difference of 0.62 mmol/L (18). Therefore, the difference between the two methods appears to be reduced when the whole or normal range of potassium concentrations is evaluated. However, the difference between the two methods increases only when evaluating the higher range of potassium concentrations, as was found in this study and by others (18).

The type of blood sample required for analysis may play a role. While POC-BGA requires a whole blood sample, laboratory auto-analysers require a serum sample. To utilise whole blood for POC-BGA, a heparinised sample is required. A study that evaluated the effects of different concentrations of liquid heparin and heparin vacutainers on the measurement of electrolytes reported that liquid formulations had a significant negative bias on measured concentrations of electrolytes (26). On the other hand, serum samples may be susceptible to pseudohyperkalaemia. Two factors that contribute to this are the absolute potassium concentrations and the number of platelets (27). In serum, during the clotting process, potassium released by platelets cause the serum potassium concentration to rise and can cause a difference between the two methods of approximately 0.3 mmol/L, even when platelet counts are within the normal range (28). Drogies *et al.* reported that the difference between the measured plasma and serum potassium concentrations were < 0.1 mmol/L in the presence of hypokalaemia, while it was > 0.5 mmol/L during hyperkalaemia (27). Therefore, an additional factor contributing to the difference in measurements identified in our study may be the inclusion of samples with only high potassium concentrations.

This study was the first to prospectively determine the agreement between POC-BGA and laboratory auto-analyser potassium concentrations in patients with hyperkalaemia. As this study was conducted using a standardised phlebotomy technique, hand-delivery of samples to the laboratory and the exclusion of patients with thrombocytosis, and hyperleukocytosis, the difference may be greater in less ideal clinical settings. Also, our results may not be generalisable since the analytic imprecision may differ between laboratories.

In conclusion, the POC-BGA is not a replacement for laboratory auto-analyser measurements but should rather be viewed as complementary, allowing for a rapid response in the emergency department. Although regression analysis indicated a proportional systematic error, on Bland Altman analysis, the mean difference appeared to remain relatively constant across the potassium range that was evaluated. Therefore, in patients presenting to the emergency department with a clinical suspicion of hyperkalaemia, POC-BGA potassium concentrations may be considered a surrogate for laboratory auto-analyser measurements once clinicians have been cautioned about this difference.

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Potential conflict of interest

None declared.

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CHAPTER 6

TESTING A NOVEL THERAPEUTIC OPTION

Bolus administration of intravenous glucose in the treatment of hyperkalemia: A randomized controlled trial

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Bolus Administration of Intravenous Glucose in the Treatment of Hyperkalemia: A Randomized Controlled Trial

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Key Words
Clinical trial · Glucose · Hyperkalemia · Hypoglycemia · Insulin

Abstract
Background: Hyperkalemia is a common medical emergency that may result in serious cardiac arrhythmias. Standard therapy with insulin plus glucose reliably lowers the serum potassium concentration ([K^+]) but carries the risk of hypoglycemia. This study examined whether an intravenous glucose-only bolus lowers serum [K^+] in stable, nondiabetic, hyperkalemic patients and compared this intervention with insulin-plus-glucose therapy. ***Methods:*** A randomized, crossover study was conducted in 10 chronic hemodialysis patients who were prone to hyperkalemia. Administration of 10 units of insulin with 100 ml of 50% glucose (50 g) was compared with the administration of 100 ml of 50% glucose only. Serum [K^+] was measured up to 60 min. Patients were monitored for hypoglycemia and EKG changes. ***Results:*** Baseline serum [K^+] was 6.01 ± 0.87 and 6.23 ± 1.20 mmol/l in the insulin and glucose-only groups, respectively ($p = 0.45$). At 60 min, the glucose-only group had a fall in [K^+] of 0.50 ± 0.31 mmol/l ($p < 0.001$). In the insulin group, there was a fall of 0.83 ± 0.53 mmol/l at 60 min ($p < 0.001$) and a lower serum [K^+] at that time compared to the glucose-only group (5.18 ± 0.76 vs. 5.73 ± 1.12 mmol/l, respectively; $p = 0.01$). In the glucose-only group, the glucose area under the curve (AUC) was greater and the insulin AUC was smaller. Two patients in the insulin group developed hypoglycemia. ***Conclusion:*** Infusion of a glucose-only bolus caused a clinically significant decrease in serum [K^+] without any episodes of hypoglycemia.

Introduction

Hyperkalemia is a frequently encountered medical emergency that can lead to life-threatening cardiac arrhythmias and therefore requires rapid and effective treatment. In hospitalized patients, hyperkalemia is often seen in individuals who are older, have impaired renal function, or are being treated with potassium supplementation or drugs which block the renin-angiotensin-aldosterone system [1, 2]. The principles of management involve protecting the heart, shifting potassium into cells, eliminating potassium from the body and treating the underlying causes of the hyperkalemia.

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Several aspects of the emergency treatment remain controversial, although regular (soluble) insulin plus glucose is usually recommended as first-line therapy in the acute management. β_2-Agonists may lower serum potassium (K^+) to a similar degree as insulin, but around one third of patients have a decline in serum K^+ that is <0.5 mmol/l, and therefore using these agents as monotherapy is not recommended [3]. The doses of β_2-agonists required to lower serum K^+ are severalfold higher than those used in acute asthma, leading to safety concerns, especially in patients who may also have cardiac disease. Sodium bicarbonate is recommended in the acute setting only if associated with a severe degree of acidosis [4]. Cation exchange resins do not significantly increase potassium excretion in the acute setting [5, 6] and have been associated with instances of colonic necrosis when used in combination with sorbitol [7–9]. They can therefore no longer be considered to be part of the standard treatment for acute hyperkalemia [3, 10, 11].

Insulin causes a shift in K^+ into cells by activating NHE-1, the Na^+/H^+ exchanger, in cell membranes [12]. The subsequent entry of Na^+ into the cell activates Na^+/K^+-ATPase, which causes the exit of 3 Na^+ and the entry of 2 K^+ with each cycle of the pump. In this way, insulin therapy rapidly and reliably lowers serum [K^+], but this comes at the cost of frequent episodes of hypoglycemia, even when glucose is given concurrently to try and prevent this complication [13–16]. Hypoglycemia is a serious and common adverse effect of insulin therapy and may manifest several hours after insulin administration [17, 18].

While earlier studies in various settings have demonstrated that oral or intravenous glucose loading can lower serum [K^+] [19–22], this has never been adopted as a component of the therapy for the emergency treatment of hyperkalemia. There have been concerns that the administration of an intravenous glucose bolus without insulin might not elicit sufficient release of endogenous insulin to cause a rapid, reliable and clinically useful degree of potassium shift into cells [3, 23, 24]. Some uremic patients may have a decreased early insulin response [25], and acutely ill patients may have α-adrenergic activation causing impaired pancreatic insulin release [26]. Another concern is that the administration of hypertonic glucose may paradoxically worsen the hyperkalemia by causing a shift of potassium out of cells [27–29]. Solvent drag of potassium-rich intracellular water into the extracellular compartment and increased leakage of potassium out of cells effected by the hypertonicity have been suggested as possible mechanisms for this phenomenon [29].

We studied the question of shifting potassium into cells in a group of hyperkalemic patients on chronic hemodialysis (HD) and compared the efficacy and safety of a glucose bolus with that of standard insulin-glucose therapy. Many of the studies which have informed the current treatment of hyperkalemia have been conducted in similar groups of patients with end-stage renal disease (ESRD). While these patients all have some degree of insulin resistance with respect to glucose homeostasis [30–32], the other actions of insulin are maintained, including the shift of potassium into cells [33].

Materials and Methods

We undertook this clinical trial in ESRD patients who were on thrice-weekly HD at the Renal Unit of Tygerberg Hospital in Cape Town, South Africa. Ethics approval was obtained from the Stellenbosch University Health Research Ethics Committee (reference No. M07/10/060). All participants gave written, informed consent. The trial adhered to the Declaration of Helsinki and was registered in the Pan African Clinical Trials registry before commencement (reference No. ATMR2009100001631792).

Participants

The study population of 10 individuals was recruited from stable nondiabetic patients who had been on chronic HD for at least 3 months. Participants prone to developing hyperkalemia were identified from their last 3 sets of routine blood results, with all having serum [K^+] exceeding 5.0 mmol/l before dialysis in each of the tests.

Study Design

A randomized, crossover, double-blind study was conducted with a washout period of at least 1 week between the two interventions for each participant (fig. 1). Simple randomization to receive insulin plus glucose or the glucose-only bolus as the first treatment was done using a computer-generated random number sequence. Allocation concealment was achieved with the use of sequentially numbered, opaque, sealed envelopes. An independent assistant prepared syringes with either 10 units of regular insulin or with an equivalent volume of saline. The participants, the treating doctor and the dialysis staff were blinded to the treatment administered.

Study Procedures

Participants were all studied in the non-fasting state on dialysis days following their longest interdialytic period. All blood samples were drawn from a cannulated arteriovenous fistula or a temporary dialysis catheter, were centrifuged promptly and processed by a single, internationally accredited laboratory. Potassium concentrations were measured by ion-selective electrode, glucose was measured by the hexokinase method and insulin by immunoassay on Roche/Hitachi Cobas® c 501 and c 601 systems. Baseline samples for potassium, glucose and insulin levels were taken. Blood pressure, heart rate and weight were documented, and a 12-lead EKG tracing recorded. The insulin, and the saline in the case of the controls, was injected into a 50-ml bag of 50% dextrose and infused rapidly at time 0. This was followed immediately by the infusion of a second 50-ml

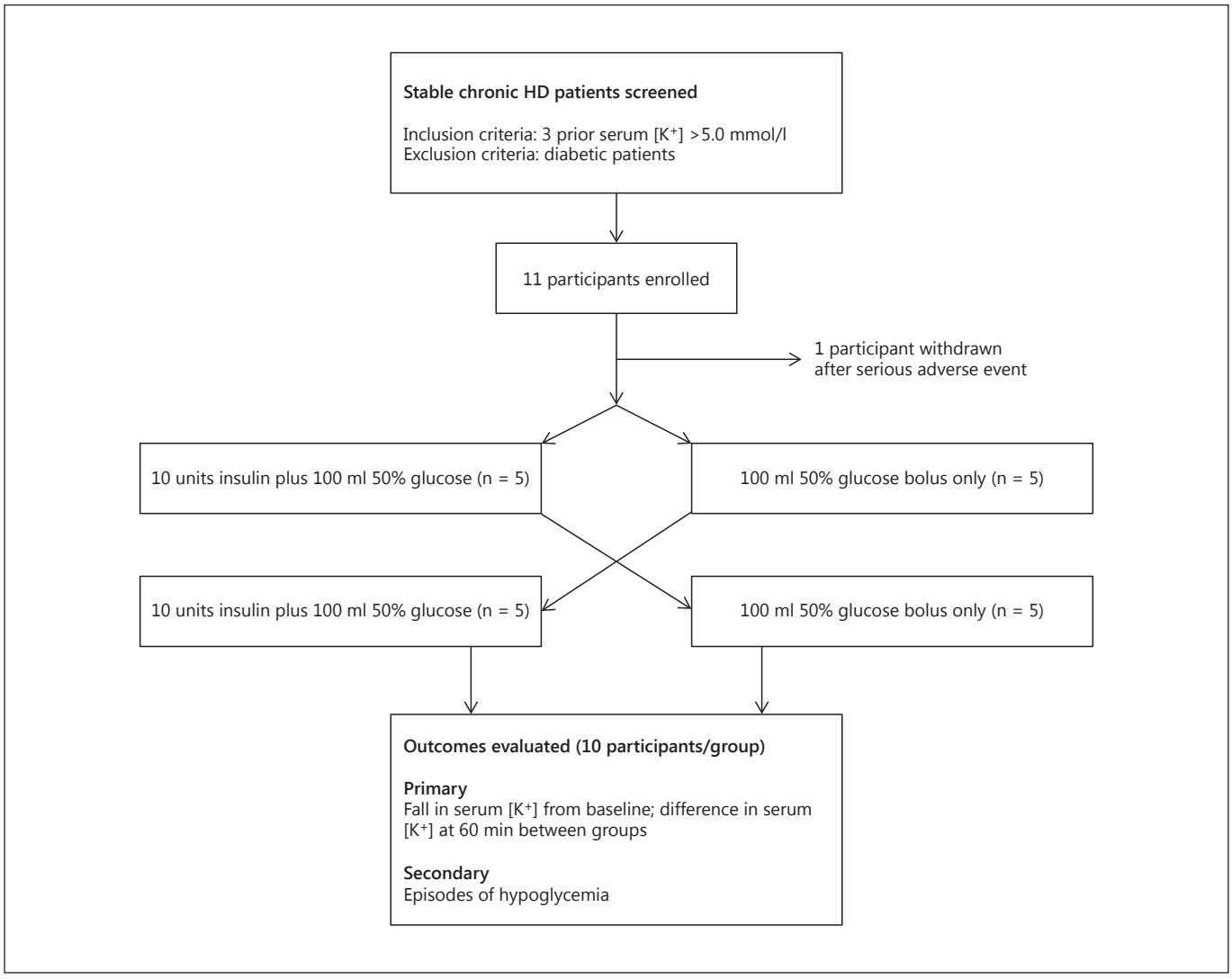

Fig. 1. Study flow diagram: in this crossover design, 10 participants completed both arms of the study and could be evaluated. The first treatment for each participant was randomly assigned, and participants and medical staff were blinded to the treatment administered. Each participant had a washout period of at least 1 week between treatment arms.

bag of 50% dextrose and then by 50 ml of normal saline to flush the giving set. The total dose of glucose administered was 50 g and the infusion of the solutions took 4–5 min. Blood samples for potassium, glucose and insulin levels were repeated after 10, 20, 40 and 60 min. Blood pressure and heart rate measurements were repeated at the same time points. Bedside blood glucose measurements were done at each time point using a Roche Accu-Chek Active® glucometer and participants were monitored for symptoms of hypoglycemia. If blood glucose fell <3.0 mmol/l or symptoms of hypoglycemia developed at any point, an additional 50-ml bolus of 50% dextrose was infused. The EKG was repeated after 60 min. EKGs were read by two of the authors (M.-Y.C. and M.R.D.) to identify changes typical of hyperkalemia, namely tall, peaked T waves, flattened or absent P waves and widening of the QRS complex.

Outcomes

The primary outcomes of interest were the magnitude of the fall in serum [K^+] from baseline values and the difference in serum [K^+] at 60 min between the two treatment groups. The secondary outcomes related to safety, namely episodes of hypoglycemia and EKG abnormalities.

Statistical Methods

Data are reported as means ± SD and statistical significance was set at $p < 0.05$.

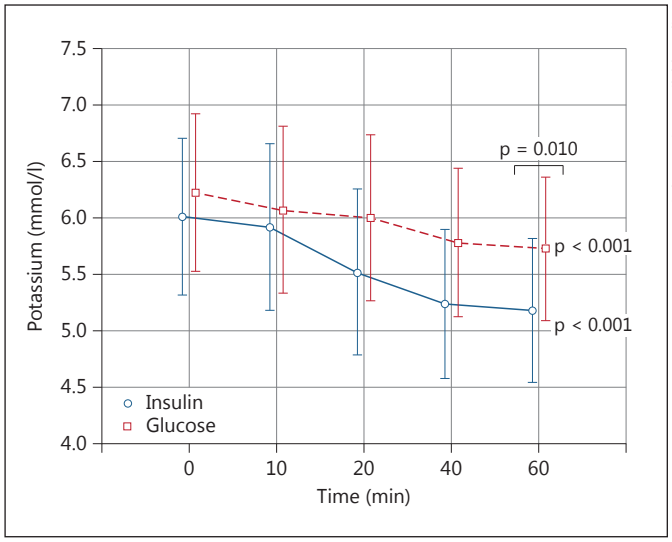

Fig. 2. Serum potassium concentration versus time: values at 60 min are significantly lower than baseline values in each treatment group ($p < 0.001$ in each case); at 60 min they are significantly lower in the insulin as compared to the glucose-only group ($p = 0.010$). Mean values with 95% confidence intervals.

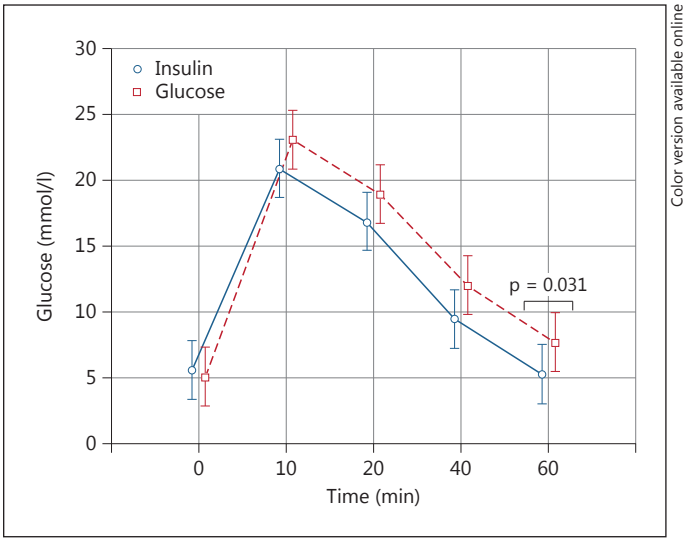

Fig. 3. Plasma glucose concentration versus time: at 60 min, but not at any other time point, the glucose concentrations were higher in the glucose-only group (7.68 vs. 5.26 mmol/l, $p = 0.031$). Mean values with 95% confidence intervals.

Table 1. Baseline characteristics of the participants (n = 10)

Baseline characteristics	Insulin-glucose	Glucose-only	p values
Males, n	5	5	
Mean age, years	40.2	40.2	
Mean potassium, mmol/l	6.01±0.87	6.23±1.20	0.45
Mean glucose, mmol/l	5.57±2.01	5.08±0.73	0.50
Mean insulin, μU/ml	28.41±32.7	21.84±18.3	0.48

Results

The baseline characteristics of the participants are summarized in table 1. The 10 participants who completed the study had a mean age of 40.2 years (range 20–54). There were equal numbers of males and females. There were 6 participants who were being treated with atenolol for hypertension during the study.

At baseline, the mean serum [K^+] was 6.01 ± 0.87 mmol/l in the insulin group and 6.23 ± 1.20 mmol/l in the glucose-only group ($p = 0.449$). At 60 min, the glucose-only group had a fall in [K^+] of 0.50 ± 0.31 mmol/l ($p < 0.001$) while in the insulin group there was a fall from baseline of 0.83 ± 0.53 mmol/l ($p < 0.001$). The insulin group had a lower serum [K^+] at 60 min as compared to the glucose-only group (5.18 ± 0.76 vs. 5.73 ± 1.12 mmol/l, respectively; $p < 0.010$; fig. 2).

There was no difference in the fall in mean serum [K^+] at 60 min between participants who were on atenolol as compared with those who were not (0.66 vs. 0.60 mmol/l, respectively; $p = 0.645$).

Analysis of individual patient data revealed that 9 of the 10 participants in the glucose-only group had a fall in serum [K^+] at 60 min while 1 participant was unchanged (the fall from baseline values ranged from 0.0 to 1.1 mmol/l). All the participants in the insulin group had a lower value at 60 min (differences ranged from 0.1 to 2.0 mmol/l). At the earliest time point (10 min), there was 1 participant in the glucose group with a higher serum [K^+] than at baseline (an increase of 0.2 mmol/l), while there were 3 participants with a rise in serum [K^+] at this time point (mean increase of 0.4 mmol/l) in the insulin group.

Plasma glucose concentrations (fig. 3) were similar at baseline in the insulin and glucose-only groups (5.57 ± 2.01 vs. 5.08 ± 0.73 mmol/l, respectively; $p = 0.500$). Glucose concentrations at 60 min were higher in the glucose-only group (5.26 vs. 7.68 mmol/l; $p = 0.031$) but not at the earlier time points. The area under the curve (AUC) was greater in the glucose-only group with a mean AUC of 857.8 ± 54.2 versus 731.0 ± 59.0 mmol·min/l ($p = 0.048$).

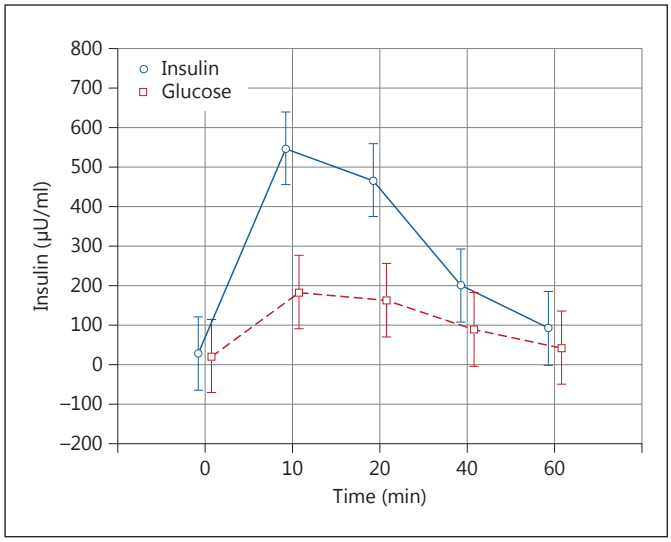

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Fig. 4. Serum insulin concentration versus time: insulin concentrations were similar at baseline in both groups (p = 0.484) but were higher in the insulin group at 10 (p = 0.002), 20 (p < 0.001), 40 (p = 0.034) and 60 min (p = 0.038). The mean AUC was greater in the insulin group (17,564.1 vs. 6,626.3 μU · min/ml, p = 0.001). Mean values with 95% confidence intervals.

Insulin concentrations (fig. 4) were similar at baseline (28.4 ± 32.7 μU/ml in the insulin group vs. 21.8 ± 18.3 μU/ml in the glucose-only group, p = 0.484) but higher at 10 min (547.5 ± 348.5 vs. 183.7 ± 128.2 μU/ml, p = 0.002), 20 min (467.4 ± 217.0 vs. 163.4 ± 99.6 μU/ml, p < 0.001), 40 min (200.6 ± 145.0 vs. 89.7 ± 40.0 μU/ml, p = 0.034) and at 60 min (92.3 ± 66.1 vs. 43.5 ± 23.4 μU/ml, p = 0.038) in the insulin group. The AUC was greater in the insulin group with a mean AUC of 17,564.1 ± 2,897.1 versus 6,626.3 ± 1,129.9 μU · min/ml (p = 0.001).

Two participants in the insulin group developed hypoglycemia. Both were using atenolol. One developed symptomatic hypoglycemia with a glucose concentration of 2.4 mmol/l at 90 min and the other developed asymptomatic hypoglycemia with a glucose concentration of 1.4 mmol/l at 60 min. They received an additional 50 ml of 50% glucose as per protocol. There were no episodes of hypoglycemia in the glucose-only group.

One participant developed pulmonary edema shortly after the administration of the study medication (insulin plus glucose). EKG and cardiac enzymes did not reveal any evidence of arrhythmia, ischemia or infarction, but echocardiography revealed hypertensive heart disease with severe diastolic dysfunction. The participant was withdrawn from the study after this serious adverse event.

All patients reported a warm or burning sensation at the site of infusion, which subsided as soon as the infusion ended.

In 5 patients, EKG changes of hyperkalemia were present at baseline on both arms of the study and in 1 patient on the occasion of the glucose arm only. Tall T waves were present in all of these cases, and decreases in T wave amplitude were observed on the 60-min EKG in all the patients after insulin administration and in 3 of the 6 patients after administration of the glucose-only bolus. A flat P wave was present in 1 patient before the glucose-only bolus; this was unchanged at 60 min. No widening of the QRS complexes was seen.

Discussion

In our study, an intravenous glucose bolus caused a clinically significant decrease in serum [K^+] concentration of approximately 0.5 mmol/l, without any incidents of hypoglycemia. These findings suggest that an intravenous infusion of glucose could be considered as a therapeutic option in the emergency treatment of hyperkalemia in settings where careful monitoring for hypoglycemia may not always be possible and where attending clinicians may prefer to avoid the risk of this serious complication altogether.

This approach of using endogenously secreted insulin to shift K^+ into cells is supported by data from a recent paper by Cheema-Dhadli et al. [34], who studied the effects of an infusion of L-lactic acid on K^+ shift in rats. They demonstrated that the liver plays a major role in removing absorbed dietary K^+ from the portal blood, thereby minimizing the risk of cardiac arrhythmia which might result if blood with a high serum K^+ concentration were delivered to the heart. The first component of the proposed mechanism is a high rate of production of L-lactic acid by enterocytes with subsequent lactic acid entry into hepatocytes on the monocarboxylic acid cotransporter [35]. The second is the release of insulin into the portal vein in response to a rise in blood glucose concentrations. These factors activate NHE-1 [36] and allow the entry of Na^+ followed by its electrogenic efflux via Na^+-K^+-ATPase, creating a more negative intracellular voltage and retaining more K^+ inside hepatocytes.

Our participants receiving insulin had higher insulin concentrations and a larger fall in serum K^+ concentration compared to those receiving glucose only. In future studies, it would be useful to study the effects of infusing larger doses of glucose to try and induce more endogenous insulin release and possibly achieve a fall in K^+ con-

Table 2. Risk of hypoglycemia with insulin therapy for hyperkalemia

Study and participants (n)	Glucose, g	Insulin, units	Glu/Ins ratio	Hypoglycemia, n (%)	ΔK^+	Details
Blumberg et al. [13] 1988 ESRD (10)	20	20	1	5 (50)	0.92	Insulin-glucose infusion at 5 mU/kg/min insulin for 60 min
Lens et al. [14] 1989 ESRD/AKI (10)	40	10	4	2 (20)	1.0	Glucose over 15 min and insulin bolus
Allon & Copkney [15] 1990 ESRD (12)	25	10	2.5	9 (75)	0.65	Insulin bolus then glucose over 5 min
Ljutic & Rumboldt [38] 1993 ESRD (9)	25	10	2.5	1 (11)	0.76	Glucose over 5 min then insulin bolus
Allon & Shanklin [39] 1996 ESRD (8)	60	20	3	0 (0)	0.85	Insulin-glucose infusion at 5 mU/kg/min insulin for 60 min
Kim [40] 1996 ESRD (8)	40	20	2	0 (0)	0.6	Insulin-glucose infusion at 5 mU/kg/min insulin for 60 min
Ngugi et al. [41] 1997 AKI/CKD (10)	25	10	2.5	2 (20)	1.14	Glucose over 15 min then insulin bolus
Mahajan et al. [16] 2001 ESRD (11)	25	12	2.1	1 (9)	0.47	Insulin-glucose infusion at 5 mU/kg/min insulin for 30 min
Chothia et al., 2014[1] ESRD (10)	50	10	5	2 (20)	0.83	Insulin-glucose over 2–3 min then glucose over 2–3 min

Data were extracted from studies on the treatment of hyperkalemia with an insulin-glucose arm where data on hypoglycemia were reported. Dosages of insulin and glucose, and changes in plasma or serum (K^+) are as at the end of 60 min. The Glu/Ins ratio refers to the dose of glucose in grams and that of insulin in international units. AKI = Acute kidney injury; CKD = chronic kidney disease.

[1] Data from the present study.

centration which is comparable to that seen when insulin is administered.

Hypoglycemia remains a common complication of insulin therapy. In a recent Japanese hospital-based survey [37], hypoglycemia was associated with serious complications, including QT prolongation and new-onset atrial fibrillation. This, at least in part, might be related to the excessive release of sympathetic hormones in response to the hypoglycemia. In studies of insulin therapy for the treatment of hyperkalemia, hypoglycemia has been documented in as many as 75% of participants (table 2). There appear to be fewer hypoglycemic events when the glucose dose is larger, when the insulin bolus is given after the glucose infusion rather than before it and when the treatment is given as a constant infusion over 60 min rather than as a bolus. Careful clinical monitoring and repeated measurements of blood glucose are recommended for several hours after insulin therapy [17, 18].

Our protocol specified a higher glucose/insulin ratio (50 g of glucose/10 units of insulin) than those used in the other studies summarized in table 2, but despite this there were hypoglycemic episodes in 2 of 10 patients. It is possible that giving the insulin after first infusing all of the glucose may have reduced the incidence of this complication.

The infusion of large amounts of hypertonic glucose without insulin carries the theoretical risk of increasing serum $[K^+]$ via the high serum osmolality, which may cause potassium-rich intracellular water to flow out of cells. In the study by Conte et al. [29], hypertonic saline caused an increase in serum $[K^+]$ independent of pH, bicarbonate concentration, anion gap, insulin concentration and urinary adrenaline and noradrenaline levels. An earlier study by Goldfarb et al. [27] examined the effect of rapid infusions of hypertonic glucose on serum $[K^+]$ and found that hyperkalemia developed in subjects with combined insulin and aldosterone deficiency but not in normal volunteers or

in diabetics with insulin deficiency alone. None of our participants had a rise in serum [K^+] at 60 min compared to baseline values. At the earliest time point, when the effect of the hypertonic infusion would be expected to be maximal, there were more patients in the insulin than in the glucose-only group with a rise in serum [K^+].

Another concern is that hypertonic solutions, with or without insulin, rapidly expand the extracellular fluid compartment, increasing the risk of pulmonary edema in patients with heart disease. This complication was seen in 1 of our participants after receiving the insulin-glucose combination.

The efficacy and safety of glucose-only boluses in treating hyperkalemia in acutely ill patients needs further investigation, and our data cannot be generalized to these patients. It is possible that in situations where α-adrenergic stimulation might be increased, e.g. in critically ill patients, this would suppress endogenous pancreatic insulin release and a glucose-only regimen might not be effective in reducing serum [K^+].

Conclusion

In stable, nondiabetic HD patients an intravenous glucose bolus caused a clinically significant decrease in serum [K^+] of 0.5 mmol/l. This provides an additional treatment option in the emergency treatment of hyperkalemia without the risk of inducing hypoglycemia. Further studies are needed to investigate the role of this intervention in acutely ill patients.

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Disclosures

No conflicts of interest to report.

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CHAPTER 7

DISCUSSION AND CONCLUSIONS

CHAPTER 7 – DISCUSSION AND CONCLUSIONS

In this concluding chapter we summarise our findings (also see Figure 1) and discuss the significance of the results with recommendations to improve the emergency management of hyperkalaemia. Finally, proposed future directions of research are outlined.

Synopsis of results

Aim 1: Determine the disease burden (Chapter 2)

At a large referral hospital, we found the incidence of hyperkalaemia to be 3.7 cases per 100 patient-years and the prevalence to be 3.7%. The presence of acute or chronic kidney disease was associated with the [K^+]. Nearly a third of the patients died in hospital, with AKI the strongest predictor of in-hospital death. Other factors associated with in-hospital death included higher [K^+], impaired kidney function, hypertension, diabetes, RAASi therapy and acute therapy for the hyperkalaemia. Patients who died were less likely to be taking RAASi therapy. The frequency of capillary blood glucose monitoring was low, as were the rates of documented hypoglycaemia.

Fourteen percent of the patients with hyperkalaemia were HIV positive. They were relatively young, mostly female, had worse kidney function, experienced fewer NCDs and were more likely to be taking trimethoprim than those who were HIV negative. There was no association of in-hospital death with HIV status.

Conclusion: The in-hospital mortality of patients with hyperkalaemia was high and was associated with AKI. Future research should focus on whether the earlier identification and effective management of patients with hyperkalaemia in association with AKI would improve outcomes.

Aim 2: Review of adverse effects of treatment (Chapter 3)

The scoping review included 62 articles and revealed an overall prevalence of hypoglycaemia of 17.2% (95% CI 16.6–17.8%). Hypoglycaemia occurred a median of 124 minutes after insulin administration (IQR 102–168 minutes). Lower insulin doses were associated with a reduced prevalence of severe hypoglycaemia (3.5% vs. 5.9%), and continuous infusion of dextrose was associated with a lower overall prevalence (3.3% vs. 19.5%). There were no differences in the prevalence when comparing insulin dose (<10

units vs. ≥10 units), rate of insulin administration (continuous vs. bolus), type of insulin (regular vs. short-acting), timing of insulin administration relative to dextrose, or the dose of dextrose (≤25 g vs. >25 g). An inverse relationship between the pre-treatment serum glucose concentration and the prevalence of hypoglycaemia was found.

Conclusion: This is the first comprehensive review of the adverse effects of insulin-based therapy for treating hyperkalaemia. Hypoglycaemia was the most frequently reported adverse effect. Future studies should focus on identifying the most effective regimen of insulin therapy to mitigate the risk of hypoglycaemia, and guidelines and educational materials should emphasize the high risk of this serious complication and the importance of carefully monitoring blood glucose concentrations.

Aim 3: Identifying knowledge gaps among clinicians (Chapter 4)

This survey assessed the knowledge of 51 medical specialists (47% nephrologists) on the emergency management of hyperkalaemia. Nephrologists were more likely to initiate therapy at a [K^+] of 6 mmol/L, whereas non-nephrologists tended to start at a lower concentration. Half the respondents regarded blood gas measurements as providing an accurate measure of [K^+]. Non-nephrologists were more likely to perform an ECG before starting treatment. All respondents regarded insulin and dextrose as the most effective and reliable means for shifting potassium intracellularly. Only one in five monitored the blood glucose concentration beyond two hours following insulin-based therapy, and one-fifth thought that hypoglycaemia was an uncommon complication if dextrose was also administered.

Conclusion: This is a first comprehensive survey regarding the management of hyperkalaemia by medical specialists. We found a wide variation in knowledge and practices. These results will assist in developing consensus-based guidelines on the management of hyperkalaemia and the knowledge gaps identified will inform the development of educational resources for clinicians and students.

Aim 4: Improving diagnostic options (Chapter 5)

Measurements of [K^+] using a point-of-care blood gas analyser (POC-BGA) were compared with measurements using a laboratory auto-analyser in a method comparison study. Using paired venous blood samples from patients with hyperkalaemia, the median laboratory auto-analyser [K^+] was 6.1 (IQR 5.9–7.1) mmol/L as compared to the POC-BGA [K^+] of 5.7 (IQR 5.5–6.8) mmol/L, with a mean difference of –0.43 mmol/L and 95% upper and lower limits of

agreement of 0.35 mmol/L and –1.21 mmol/L, respectively. Importantly, the mean difference remained constant across the [K^+] range that was evaluated.

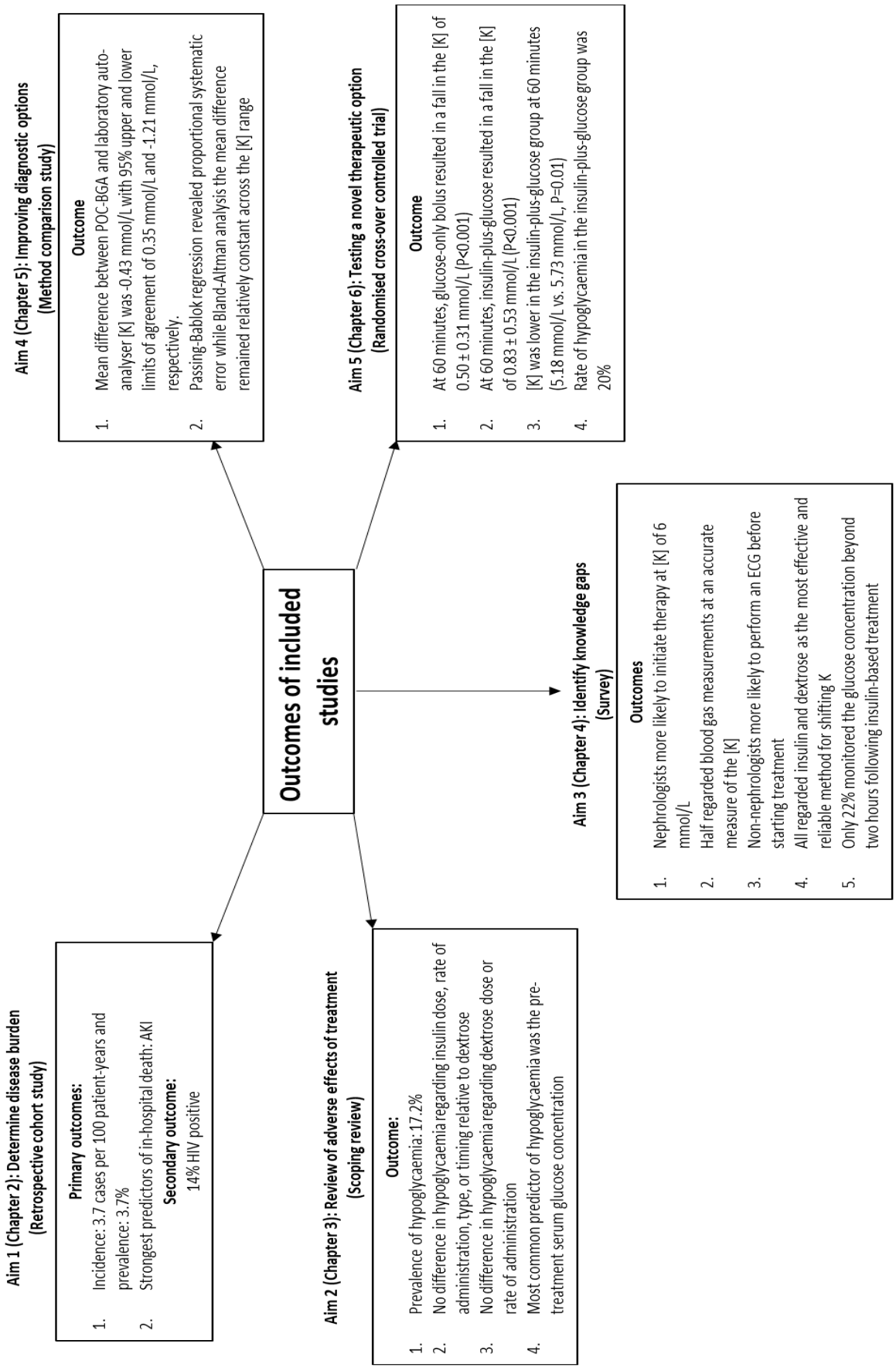
Conclusions: This is the first prospective method comparison study comparing the POC-BGA [K^+] values with laboratory measurements in patients with hyperkalaemia and kidney disease. We found a systematic bias of –0.4 mmol/L, which remained relatively constant across the hyperkalaemic range. POC-BGA [K^+] measurements (with adjustment for this bias) can therefore be used, allowing clinicians in the emergency unit to make a more rapid diagnosis of hyperkalaemia and to initiate treatment more promptly.

Aim 5: Testing a novel therapeutic option (Chapter 6)

In a randomised, cross-over clinical trial, the administration of 10 units of insulin with 100 mL of 50% dextrose (50 g) was compared with the administration of 100 mL of 50% dextrose only. At 60 min, the dextrose-only group recorded a fall in [K^+] of 0.50 ± 0.31 mmol/L. In the insulin group, there was a decline of 0.83 ± 0.53 mmol/L at 60 min and a lower serum [K^+] at that time compared to the dextrose-only group (5.18 vs. 5.73 mmol/L; P = 0.01). Two patients in the insulin group developed hypoglycaemia.

Conclusion: This is the first RCT comparing a dextrose-only bolus to insulin-plus-dextrose therapy for the management of hyperkalaemia. We have demonstrated that a dextrose-only bolus is effective for treating hyperkalaemia without any risk of hypoglycaemia. This is a new and valuable treatment option, which would be especially relevant in resource-constrained settings where careful monitoring of blood glucose may not be possible.

Figure 1. Summary of findings.



Implications and recommendations

We found a lower prevalence of hyperkalaemia in hospitalised adult patients (3.7%) compared to a recent systematic review in which the reported global prevalence was more than double that of ours and the prevalence from African studies more than 10 times greater [1]. The populations in these studies were small and included convenience samples at high risk for the development of hyperkalaemia. The reported prevalence from Africa (36.7%) was therefore likely an overestimation. Our study is the first to report on the incidence of hyperkalaemia from Africa, which proved to be lower than global rates [1]. Possible reasons may include the exclusion of patients with pseudohyperkalaemia and patients on kidney replacement therapy (KRT).

Kidney disease (87%), diabetes (28%) and hypertension (53%) were the leading comorbid diseases in patients with hyperkalaemia. Since NCDs in sub-Saharan Africa have been predicted to increase in coming years [2], a parallel rise in the burden of hyperkalaemia can be expected. Healthcare providers at all levels of care need to anticipate this complication and be conversant with the optimal management strategy. Wherever possible, RAASi therapy should be continued to ensure the best long-term outcomes for patients with underlying cardiovascular and kidney disease [3].

We found a high mortality in our study sample (29%), comparable to previous reports [4]. AKI was the strongest predictor of in-hospital death. Others have reported similar associations [5, 6]. This may be related to late presentation, possibly due to the availability of healthcare services, especially in remote areas. The centralisation of acute dialysis services in large cities may result in the late initiation of dialysis therapy in patients referred from outlying centres. Another predictor of death was the $[K^+]$ value. At the lowest $[K^+]$ of 5.5 mmol/L, the mortality was 10%, and this rate increased progressively in tandem with the increase in $[K^+]$. Healthcare providers should be aware that even mild elevations in $[K^+]$ are associated with poor short-term outcomes and should be responded to as a matter of urgency.

Since mortality can be high, especially within the first 24 hours of diagnosing hyperkalaemia, earlier diagnosis may expedite the initiation of therapy. In the emergency department, an ECG and POC-BGA $[K^+]$ measurements are investigations that may assist with rapid diagnosis. Our survey indicated that two-thirds of specialists routinely performed an ECG in patients with hyperkalaemia, although three-quarters did not believe that there was a good correlation between the $[K^+]$ and the presence of ECG changes. This view is supported by

evidence that the ECG has poor diagnostic sensitivity [7]. On the other hand, only half considered POC-BGA measurements as accurate [8]. Since there are often delays in reporting the laboratory [K^+], utilising POC-BGA measurements may shorten the time to initiating therapy. We identified a systematic negative bias between POC-BGA and laboratory auto-analyser measurements in patients with hyperkalaemia. The mean difference remained relatively constant across the hyperkalaemic range [9] and we therefore recommend that POC-BGA [K^+] measurements be used, after adjusting for this bias, so that treatment can be initiated more promptly.

The use of RAASi therapy was less frequent in patients who died. This may have been the result of fewer comorbidities such as hypertension, diabetes, and CKD. On the other hand, RAASi therapy may have been discontinued because of the development of hyperkalaemia. There was a survival benefit when RAASi therapy was continued despite hyperkalaemia, and this finding has been reported by others [10]. There is therefore an urgent need to expedite the registration and accessibility of novel potassium-binding resins such as patiromer [11] and sodium zirconium cyclosilicate [12] in South Africa, so that patients who require RAASi therapy may continue to gain from its beneficial effects without the risks related to hyperkalaemia.

Nearly 14% of our patients with hyperkalaemia were HIV positive. This mirrors the national HIV prevalence in South Africa [13]. Hyperkalaemia in HIV patients was associated with more severe AKI, and trimethoprim prescription was more frequent. Indications included either *Pneumocystis jiroveci* pneumoniatreatment or as prophylaxis, suggesting late HIV diagnosis. Despite South Africa having the largest antiretroviral therapy (ART) programme in the world, the diagnosis of HIV is often made late. Improving access to health care for patients living in rural areas and strengthening HIV prevention and screening programmes may result in the early initiation of ART and a reduction in the use of trimethoprim.

More patients who died received acute therapy for hyperkalaemia despite the absence of differences in their [K^+] values. We speculate that more severe illness and more ECG changes or arrhythmias may have prompted the initiation of treatment. The frequency of capillary blood glucose monitoring was poor and, consequently, the frequency of patients identified with hypoglycaemia was low. This was not surprising, since our survey also found a low frequency of capillary blood glucose monitoring by medical specialists, with only 22% checking it at three hours following insulin-based therapy. More than one in five considered hypoglycaemia to be an uncommon complication of insulin-based therapy when dextrose was also administered [8]. A systematic review found that hypoglycaemia may occur in up to

30% of patients when 25 g of dextrose is used with insulin-based therapy [14], while our scoping review found a prevalence of 17%. Since 90% of patients in our cohort received treatment with 25 g of dextrose, a relatively low dose, it is likely that healthcare providers missed episodes of hypoglycaemia. Based on our epidemiological study as well as our survey [8], there is a need to improve the knowledge of healthcare workers on several aspects of the emergency management of hyperkalaemia, particularly in relation to the use of insulin-based therapy.

The optimal regimen of insulin and dextrose therapy for the management of hyperkalaemia is still unclear. It should be one that maximally reduces the [K^+] while mitigating the risk of hypoglycaemia. Many recommendations are based on observational studies with a high risk of bias [14]. Only three RCTs have been performed, with only one (our study, Chapter 6) regarded as having a low risk of bias [14,15]. We demonstrated that an intravenous dextrose-only bolus causes a clinically significant decrease in the serum [K^+], without any episodes of hypoglycaemia. This is an attractive treatment option because monitoring of the glucose concentration may not be adequate in busy, resource-limited, emergency departments with frequently understaffed nursing personnel. Since our patients were clinically stable, it remains to be determined how this regimen would perform in acutely ill patients who may have reduced endogenous insulin release because of the increased sympathetic effect on pancreatic beta cells.

Although insulin-plus-dextrose therapy caused a greater decline in the [K^+], 20% of patients developed hypoglycaemia. This occurred despite administering 50 g of dextrose. Our scoping review also found no difference in the prevalence of hypoglycaemia based on the dextrose dose. Therefore, the dose of dextrose does not seem to attenuate the risk of hypoglycaemia when using insulin-based therapy; however, a continuous infusion of dextrose was associated with a reduced risk. Additionally, our scoping review found that lower doses of insulin were associated with reduced episodes of severe hypoglycaemia. Since there was no difference in treatment efficacy regarding the dose of insulin used, future studies should investigate lower doses of insulin or a weight-based insulin regimen along with a continuous infusion of dextrose.

Of concern, is the volume of dextrose infused. In our RCT, a patient with hypertensive heart disease and fluid overload developed pulmonary oedema. The volume administered as well as the hypertonic nature of the dextrose solution may have rapidly expanded the extracellular fluid compartment, resulting in the pulmonary oedema. Since hyperkalaemia frequently occurs in patients with kidney disease who may be volume overloaded, healthcare

providers must consider these factors when deciding on the volume of dextrose administered. A theoretical regimen has been proposed consisting of a hybrid of bolus and continuous infusion of insulin along with a continuous infusion of 10% dextrose [16].

We created a pocket guide (Figure 2), based on our findings, that can be used by clinicians confronted with the emergency management of hyperkalaemia.

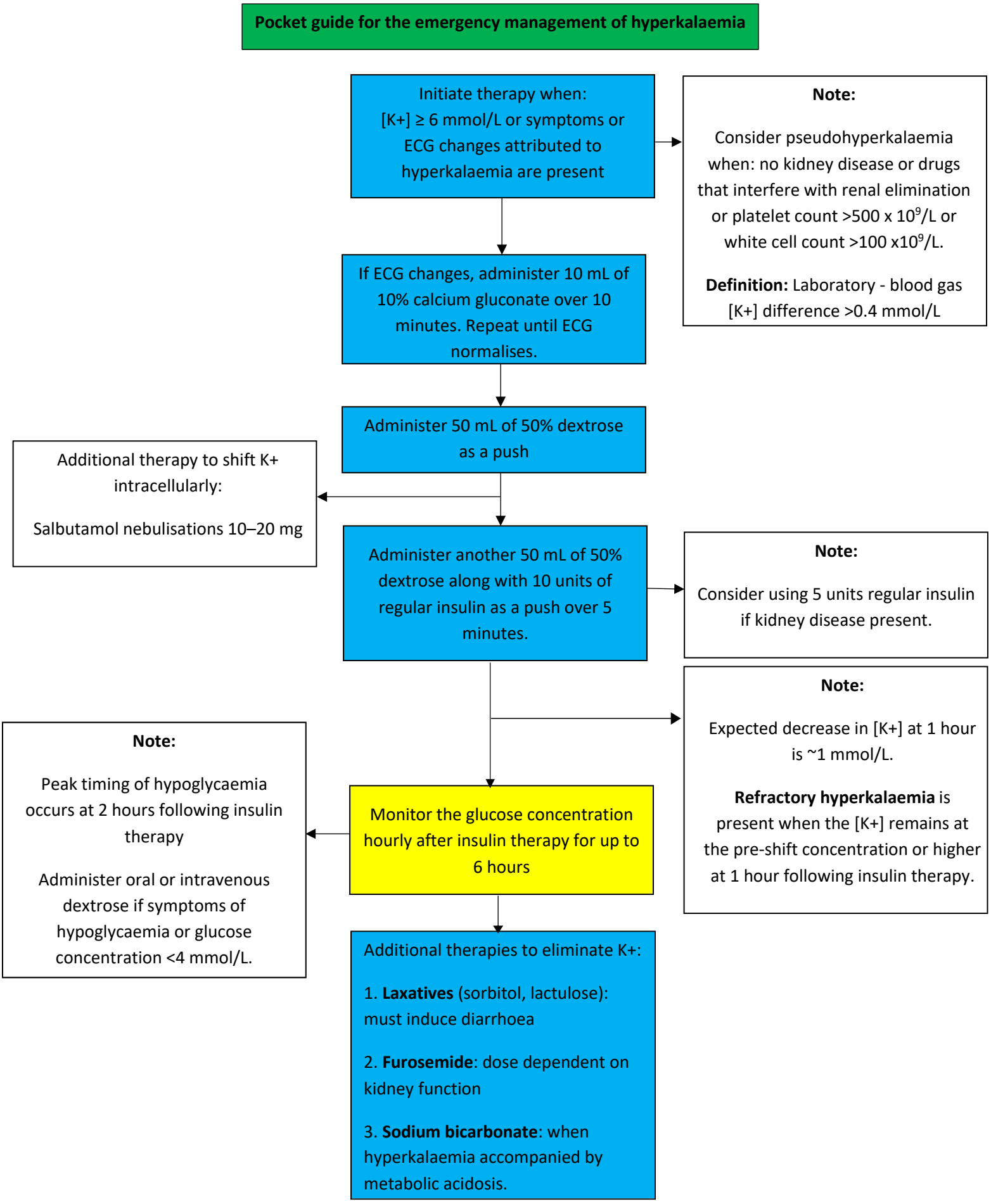
Future directions

Future research should investigate whether earlier identification and treatment of patients with hyperkalaemia in association with AKI will improve outcomes. Since acute haemodialysis services in the South African public healthcare sector are mainly available at tertiary centres, we should promote the use of acute peritoneal dialysis at peripheral centres. In 2012, the Saving Young Lives project was launched to address the lack of acute dialysis services in low-resource settings by utilising peritoneal dialysis. Impressive results have been reported from several African countries [17] and this model could be implemented and evaluated in peripheral and rural South African settings.

The wide variation in knowledge and practice patterns by medical specialists regarding the emergency management of hyperkalaemia needs to be addressed through the development of consensus-based guidelines which will assist in unifying practice and may improve outcomes. We will be conducting a workshop at the South African Renal Congress at the end of May 2022 to address the knowledge gaps we have identified, with the intention of building consensus on the optimal management of hyperkalaemia.

More high-quality RCTs are needed to identify the optimal regimen of insulin and dextrose for shifting potassium intracellularly, while mitigating the risk of hypoglycaemia. These trials should focus on the doses (≥10 units vs. <10 units) of insulin, the rate of insulin administration (bolus vs. continuous infusion vs. hybrid regimen), and the dose (25 g vs. >25 g) and rate of dextrose administration (bolus vs. continuous infusion).

Figure 2. Pocket guide for the emergency management of hyperkalaemia



Concluding remarks

Our research has contributed new insights into the occurrence of hyperkalaemia in hospitalised adult patients in an African setting. This will heighten awareness of the condition, promote targeted screening of at-risk patients, and allow prompt and improved treatment of the hyperkalaemia as well as the underlying comorbid conditions. We have highlighted the importance of hypoglycaemia following insulin-based therapy and have identified risk factors and made treatment recommendations so that the frequency of this serious adverse effect may be reduced. We have also identified knowledge gaps among healthcare providers which can now inform the development of clinical guidelines and educational resources. Clinicians can confidently use POC-BGA [K^+] measurements to diagnose hyperkalaemia, which will shorten the time to treatment. Finally, in a high-quality clinical trial, we demonstrated the efficacy and safety of a novel treatment for the management of hyperkalaemia, a dextrose-only bolus, that can be used to treat hyperkalaemia without any risk of hypoglycaemia. This is especially important in resource-constrained environments where frequent monitoring of capillary blood glucose cannot be performed after insulin therapy.

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APPENDIX 1

LIST OF PRESENTATIONS

LIST OF PRESENTATIONS

1. MY Chothia, ML Halperin, M Rensburg, MS Hasan, MR Davids. Efficacy of glucose versus glucose plus insulin in the treatment of hyperkalaemia. American Society of Nephrology Congress, Denver, Colorado, November 2010. (Poster)
2. P Kassum, A Zemlin, MY Chothia. Agreement between point-of-care blood gas analyser and laboratory auto-analyser in patients with hyperkalaemia. African Association of Nephrology Congress 2019, Mombasa. (Poster)
3. MY Chothia, ML Halperin, M Rensburg, MS Hasan, MR Davids. Efficacy of glucose versus glucose plus insulin in the treatment of hyperkalaemia. Annual Academic Day, Stellenbosch University, 2010. (Oral)
4. P Kassum, MY Chothia. Agreement between point-of-care blood gas analyser and laboratory auto-analyser in patients with hyperkalaemia. Annual Academic Day, Stellenbosch University, 2019. (Poster)
5. MY Chothia, UME Chikte, MR Davids. The development of a questionnaire evaluating knowledge of the pharmacological management of hyperkalaemia by junior doctors using a modified Delphi technique. South African Association of Health Educationalists Virtual Conference, 2021. (Poster)
6. P Kassum, A Zemlin, MY Chothia. Agreement between point-of-care blood gas analyser versus laboratory auto-analyser in patients with hyperkalaemia. Department of Medicine Research Day 2019. (Oral)
7. MY Chothia. Current trends in the management of acute hyperkalaemia, Nigerian Association of Nephrology – Young Nephrologists Committee, 18 May 2021. (Oral)
8. MY Chothia. Controversies in the emergency management of hyperkalaemia. South African Renal Society Congress, Cape Town, 2016 (Oral)
9. MY Chothia. The emergency pharmacological management of hyperkalaemia. UCT and US Physician’s Refresher Course, River Club, 21 February 2020. (Oral)
10. MY Chothia. An update on hyperkalaemia. South African Nephrology Society Update Course, 2021. (Oral)

11. MY Chothia. Building consensus-based guidelines for the acute management of hyperkalaemia. South African Nephrology Society Congress, May 2022. (Oral)
12. MY Chothia. Diagnosis and management of hyperkalaemia. South African Nephrology Society Congress, May 2022. (Oral)
13. MY Chothia, T Humphrey, A Schoonees, UME Chikte, MR Davids. Hypoglycaemia due to insulin therapy for the management of hyperkalaemia in hospitalised adult patients: A scoping review. South African Nephrology Society Congress, May 2022. (Poster)

APPENDIX 2

SUPPLEMENTARY PUBLICATIONS

SUPPLEMENTARY PUBLICATIONS

1. MY Chothia, MR Davids. BRASH syndrome: an emerging emergency. Pan Afr Med J Clin Med 2020; 4:128.

2. T Humphrey, MR Davids, MY Chothia, R Pecoits-Filho, C Pollock, G James. How common is hyperkalaemia? A systematic review and meta-analysis of the prevalence and incidence of hyperkalaemia reported in observational studies. Clin Kidney J 2021, 15(4):727-737.

Article

PAMJ Clinical Medicine

Case report

BRASH syndrome: an emerging emergency

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BRASH syndrome: an emerging emergency

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Abstract

BRASH syndrome (bradycardia, renal failure, atrioventricular nodal (AVN) blockers, shock and hyperkalaemia) is an emerging and distinct condition that occurs due to the synergistic effects of hyperkalaemia and AVN blockers on the heart. Only a few case reports have been described in the medical literature since 2016. We present an 88-year-old woman, known with hypertension, stage 5 chronic kidney disease (not on dialysis) and paroxysmal atrial fibrillation that presented with a history of four syncopal episodes in the past 2-months and had symptoms of heart failure for 1-day. Clinical examination revealed a blood pressure of 105/60 mmHg and a regular pulse rate of 31 beats per minute. Laboratory potassium concentration was 6.7 mmol/L and creatinine was 318 µmol/L. An electrocardiogram revealed a sinus bradycardia without features suggestive of hyperkalaemia. A diagnosis of BRASH syndrome was made. The patient received treatment

addressing multiple factors involved in the pathogenesis of the syndrome and responded favourably. She was discharged 1-week later. In patients with syncope, BRASH syndrome should be considered when bradycardia is associated with hyperkalaemia, along with a history of AVN blocker use. It is important to recognise so that appropriate therapy can be instituted that addresses all the elements of the syndrome, rather than focusing on a single component.

Introduction

BRASH syndrome (bradycardia, renal failure, atrioventricular nodal (AVN) blockers, shock and hyperkalaemia) is an emerging condition that occurs due to the synergistic effects of hyperkalaemia and AVN blockers on the heart [1]. It was first formally described by Farkas in 2016 where he described an elderly woman with unexplained refractory multiorgan failure and subsequently identified beta-blocker toxicity as the culprit [2]. The syndrome is a distinct entity that lies at the epicenter along a continuum, with isolated hyperkalaemia at one end of the spectrum and AVN blocker toxicity at the other. The typical patient at risk for the syndrome is an elderly patient with underlying heart disease and poor kidney reserve receiving treatment with AVN blocking agents such as beta-blockers (BB), and non-dihydropyridine calcium channel blockers (CCB) such as verapamil and diltiazem [2]. The most common precipitant is thought to be hypovolaemia. A study that investigated consecutive elderly patients requiring urgent transvenous cardiac pacing for bradyarrhythmias reported that it developed more frequently during the summer months and attributed hypovolaemia as the trigger for this phenomenon [3]. Other triggers include increasing doses of blood pressure medication, the addition of/or increasing doses of renin-angiotensin aldosterone system inhibitors (RAASi) and any cause of acute kidney injury [1,2]. In clinical practice, it may be difficult to distinguish the syndrome from the isolated effects of hyperkalaemia or AVN blockers. Clues that should raise suspicion of BRASH syndrome include bradycardia in conjunction with hyperkalaemia in the absence of classic electrocardiographic features of hyperkalaemia [1,4] and occasionally, a dramatic response to intravenous calcium [1]. We report on an elderly woman that presented with multiple episodes of syncope and heart failure a few months after restarting BB therapy for paroxysmal atrial fibrillation and was subsequently diagnosed and treated for BRASH syndrome.

Patient and observation

An 88-year-old woman, known with hypertension, stage 5 chronic kidney disease (not on dialysis) and paroxysmal atrial fibrillation (PAF), presented with a history of four syncopal episodes in the past 2-months and currently had dyspnoea and lethargy for 1-day. Prior to the current presentation, it was noted that the patient presented with bradycardia 4-years ago, which resolved following cessation of atenolol; however, 2-months before this admission, atenolol 50 mg daily was restarted by her local clinic for PAF. Other chronic medication included furosemide 80 mg twice daily, spironolactone 25 mg daily, losartan 50 mg daily, amlodipine 10 mg daily and warfarin.

Clinical examination revealed a blood pressure of 105/60 mmHg (mean arterial pressure of 75 mmHg), a regular pulse with a rate of 31 beats per minute and body temperature was 36.7°C. Hydration status was thought to be normal. She had features suggestive of left-sided heart failure. Pertinent laboratory results were as follows: sodium 136 mmol/L (normal range: 136-145 mmol/L), potassium 6.7 mmol/L (normal range: 3.5-5.5 mmol/L) , urea 25.6 mmol/L (normal range: 2.1-7.1 mmol/L), creatinine 318 µmol/L (normal range: 49-90 µmol/L) (estimated glomerular filtration rate of 11 mL/min/1.73 m^2), calcium 2.17 mmol/L (normal range: 2.20-2.55 mmol/L), haemoglobin 10.2 g/dL (normal range: 12-15 g/dL), TSH 1.83 mIU/L (normal range: 0.27-4.20 mIU/L) and high-sensitivity troponin 46 ng/L. Her electrocardiogram indicated a severe sinus

bradycardia without any classic features of hyperkalaemia (Figure 1).

The constellation of bradycardia, renal failure, use of a BB, hypotension (shock) and severe hyperkalaemia was diagnostic of BRASH syndrome. The patient was admitted to our high care unit for continuous cardiac telemetry. Her chronic medication was stopped including atenolol. On days 1 to 3, the patient received multiple doses of 10 mL of 10% calcium gluconate intravenously (IV) without any improvement in the heart rate. During the same period, frequent potassium shifting using 10 units of rapid-acting insulin along with 50 mL of 50% glucose were also utilised. One liter of isotonic sodium bicarbonate was administered over 24 hours on day 3 of hospitalisation, along with furosemide 40 mg twice daily IV and oral lactulose 10 mL thrice daily to eliminate potassium from the body. Her kidney function improved with isotonic IV fluids (Figure 2). The patient displayed a good response to treatment (Figure 2). She was advised to avoid future use of any beta-blockers and was discharged 1-week following hospitalisation.

Discussion

Patients with BRASH syndrome may present along a spectrum, from a coincidental finding of bradycardia to multiorgan failure [1]. Our patient presented with a history of 4 syncopal episodes and heart failure. Syncope seems to be the most common initial symptom of BRASH syndrome. A recent clinical review found that 13 of 23 patients (56.5%) presented with either presyncope or syncope, while the remaining patients presented with dyspnoea, diaphoresis, chest pain, weakness or lethargy in isolation or in combination with presyncope/syncope [1].

Little is known regarding its epidemiology; however, older age, poor kidney function, use of AVN blockers such as BBs and CCBs, as well as RAASi´s are common findings in a recent review of 23 cases [1]. In the latter series [5-21], the average age was 67.5 years (range 24 - 97 years). Thirteen patients were using CCBs and/or BBs in combination with RAASi´s, while 10 patients were using CCBs or BBs in isolation. Clinically, the average heart rate was 32 beats per minute (range 20 - 56 beats per minute) and the average mean arterial pressure was 62 mmHg (range 40 - 131 mmHg). For the laboratory findings, the average serum potassium concentration was 6.9 mmol/L (range 5.6 - 10.1 mmol/L) and the average serum creatinine was 260 µmol/L (range 115 - 751 µmol/L). The creatinine concentration was not reported in 4 patients because they were receiving dialysis. All these findings were present in our patient. Since elderly patients are more likely to be hypertensive, and have underlying heart and/or kidney disease, it is not surprising that BRASH syndrome is more likely to develop in this group of patients. The latter risk factors along with the prescription of antihypertensives (CCBs, BBs and RAASi´s), anti-heart failure (BBs and RAASi´s) and renoprotective drugs (RAASi´s), creates the perfect storm.

Regarding the pathogenesis, preceding renal hypoperfusion due to volume depletion from any cause, leads to kidney failure or exacerbates existing kidney disease [22]. This causes reduced renal elimination of both AVN blockers as well as potassium. Bradycardia develops due to the ensuing hyperkalaemia as well as the toxic effect of drugs on the AV node [1]. The bradycardia in turn further reduces kidney perfusion due to a reduction in cardiac output, resulting in a vicious cycle. Although kidney failure may prolong the half-life of AVN blockers that are renally eliminated, this mechanism along with RAASi are contributary and are not required for the syndrome to develop. Since volume status was thought to be normal in our patient, the negative inotropic and chronotropic effects of the BB was thought to decrease the effective arterial blood volume, reducing kidney perfusion resulting in acute-on-chronic kidney failure. The latter reducing the kidney´s ability to eliminate both the BB and potassium.

A common mistake is focusing on a single aspect of the syndrome, rather than addressing all the factors involved the pathogenesis. The key to

management is a multipronged approach which includes stopping the offending agent/s such as BBs and/or CCBs, instituting general principles for the management of hyperkalaemia, management of the bradycardia and fluid resuscitation [1]. Specifically, repeated doses of intravenous calcium salts, beta-2 agonist nebulisations and isotonic sodium bicarbonate should be considered for the management of hyperkalaemia. As alluded to previously, there may be a dramatic response to IV calcium with improvement of the bradycardia as well as cardiac inotropy. Repeated doses of IV calcium should be administered until a chronotropic response occurs. However, in the absence of a response, there should be a low threshold for intravenous adrenaline [1]. This has the advantage of increasing the heart rate, as well as shifting potassium intracellularly. Since hypovolaemia plays a pivotal role, isotonic sodium bicarbonate will improve volume status and therefore kidney perfusion, while simultaneously improving metabolic acidosis and hyperkalaemia. Most patients respond well to these general management principles without the need for more aggressive therapies. If these measures are not successful, then more advanced therapies should be considered. These include haemodialysis, IV lipid emulsions, IV glucagon and high-dose insulin and glucose, and transdermal or transvenous cardiac pacing [1,23]. Although our patient did not respond to repeated doses of IV calcium, she remained haemodynamically stable, and a decision was made not to use adrenaline. The hyperkalaemia as well as the acute kidney injury responded well to multiple doses of IV insulin and glucose, as well as the isotonic fluids including isotonic sodium bicarbonate.

Conclusion

In patients with syncope, BRASH syndrome should be considered when bradycardia is associated with hyperkalaemia, without classic ECG changes, along with a history of AVN blocker use. It is important to recognise so that appropriate therapy can be instituted that addresses all the elements of the syndrome, rather than focusing on a single component.

Competing interests

The authors declare no competing interests.

Authors' contributions

MYC was involved the clinical management of the patient and drafted the first version of the manuscript. MYC and MRD revised and approved the final version of the manuscript. All authors have read and agreed to the final manuscript.

Figures

Figure 1: the electrocardiogram at admission showing sinus bradycardia without classic features of hyperkalaemia

Figure 2: the average daily heart rate, serum creatinine and potassium concentration during admission (D-day)

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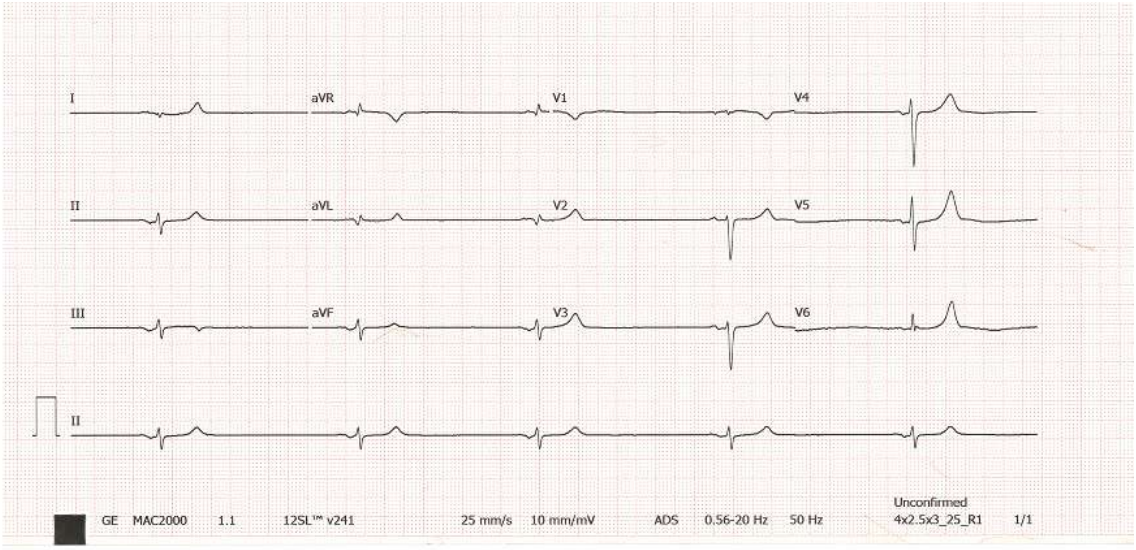

Figure 1: the electrocardiogram at admission showing sinus bradycardia without classic features of hyperkalaemia

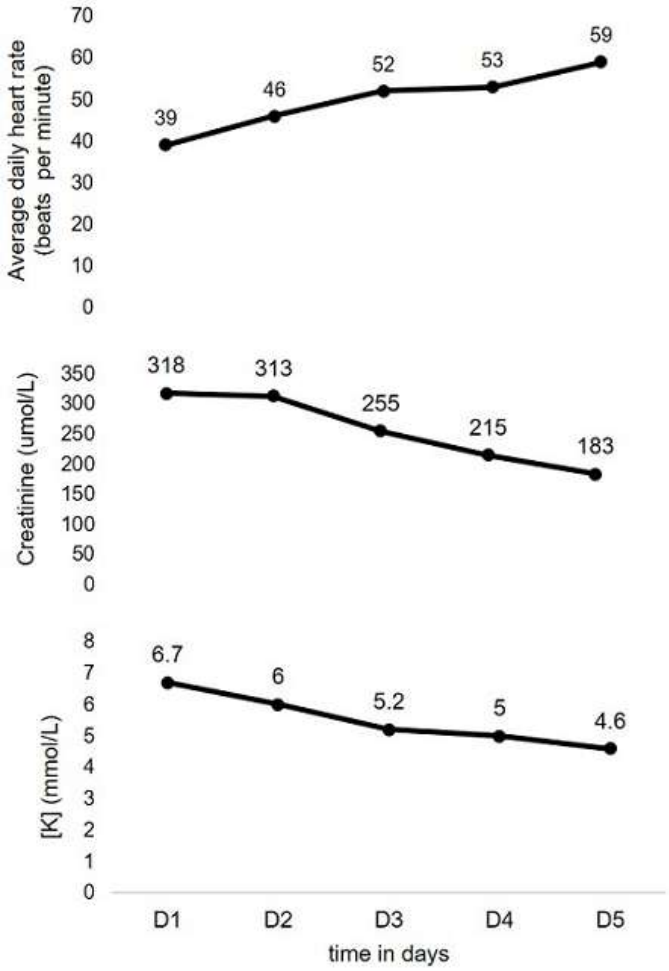

Figure 2: the average daily heart rate, serum creatinine and potassium concentration during admission (D-day)

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ORIGINAL ARTICLE

How common is hyperkalaemia? A systematic review and meta-analysis of the prevalence and incidence of hyperkalaemia reported in observational studies

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ABSTRACT

Background. The prevalence and incidence of hyperkalaemia, a potassium abnormality that can potentially have life-threatening consequences, are unclear.

Methods. The objective was to provide the most comprehensive overview of the epidemiology of hyperkalaemia to date within the general population, across different continents, in different healthcare settings and within pre-specified subgroups. Embase and MEDLINE were searched from database inception to 2 February 2021 using the Ovid SP platform. Relevant congress proceedings from 2018 to 2020 were also reviewed for inclusion. There was no language constraint applied. Observational studies from any time period and language reporting prevalence or incidence of hyperkalaemia within both adult and paediatric populations. Four investigators independently screened abstracts and assessed study quality of those meeting the pre-determined inclusion/exclusion criteria. Data extraction was conducted by the lead author with oversight from the senior author and data were pooled using a random-effects model. The measures assessed were the prevalence and incidence of hyperkalaemia. Prevalence was reported as a percentage, whilst incidence was reported as the rate per 100 person years.

Results. In total, 542 articles were included from an initial search of 14 112 articles. Across all adult studies, we report a prevalence of hyperkalaemia (by any definition/threshold) of 6.3% [95% confidence interval (CI): 5.8–6.8%], with an incidence of hyperkalaemia in the adult population of 2.8 (2.3–3.3) cases per 100 person years. Prevalence within the general population was 1.3% (1.0–1.8%), whilst incidence was 0.4 (0.2–0.8) cases per 100 person years. There was a variation by sex with a prevalence of 6.3% (4.9–8.0%) in males and 5.1% (4.0–6.6%) in females. Prevalence also varied according to the definition/threshold of hyperkalaemia used: >5 mmol/L—8.0% (7.2–8.9), ≥5.5 mmol/L—5.9% (3.5–10.0) and ≥6.0 mmol/L—1.0% (0.8–1.4); hyperkalaemia (by any definition/threshold) was highest amongst patients with end-stage kidney disease (21.5%; 18.3–25.3), kidney transplant patients (21.8%; 16.1–29.5) and patients with acute kidney injury (24.3%; 19.3–30.7).

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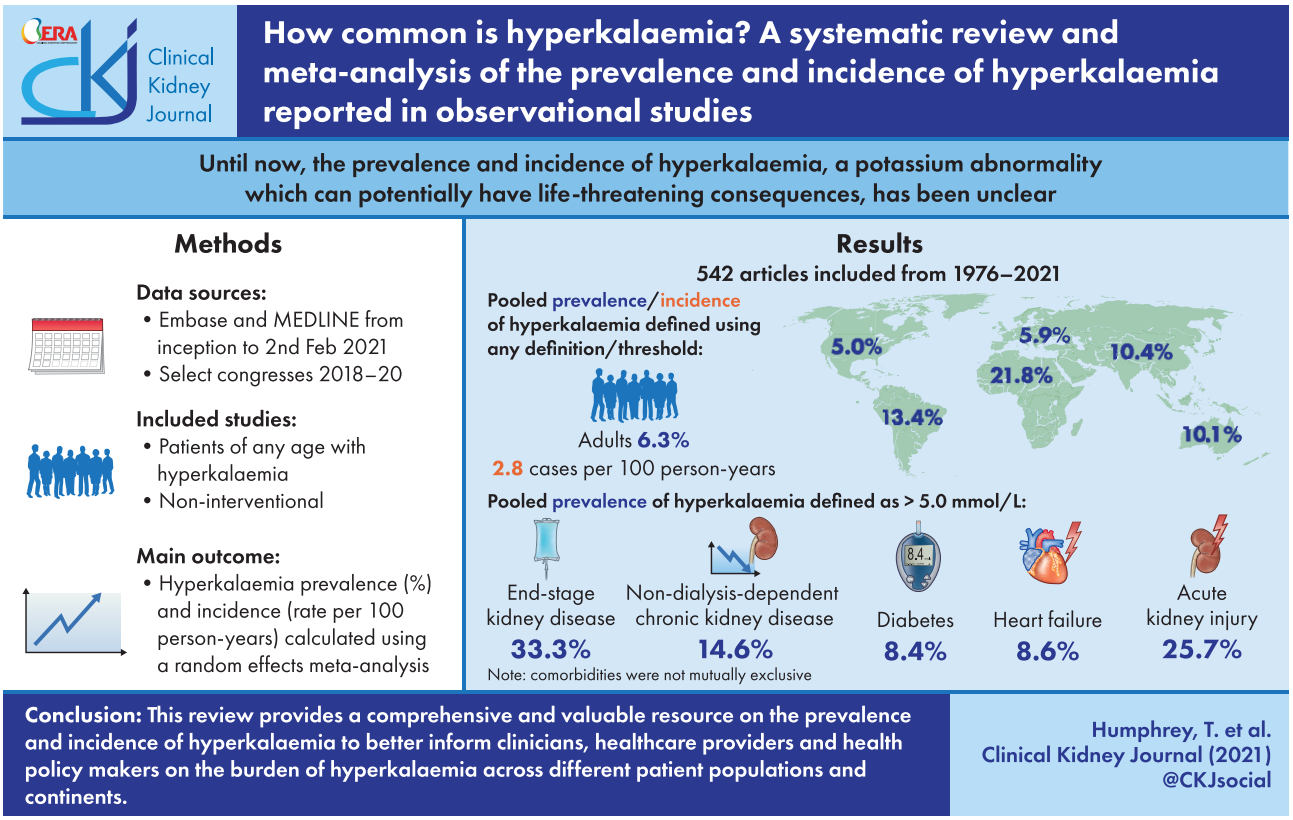
Conclusions. This novel review provides a comprehensive and valuable resource on the prevalence and incidence of hyperkalaemia to better inform clinicians, healthcare providers and health policy makers on the burden of hyperkalaemia across different healthcare settings, patient populations and continents.

GRAPHICAL ABSTRACT



Keywords: hyperkalaemia, incidence, meta-analysis, prevalence, systematic literature review

INTRODUCTION

Hyperkalaemia (HK) is the term used to describe raised serum potassium (sK^+) concentration within the blood. It is often classified as mild (>5.0–5.9 mmol/L), moderate (6.0–6.4 mmol/L) and severe (≥6.5 mmol/L) [1].

When classifying severity of HK, the rate of change in sK^+ and the presence of electrocardiogram (ECG) changes are of clinical importance [1] since it is the sK^+ concentration that determines the resting membrane potential of cells. When sK^+ is elevated, it can impair muscle function and importantly can cause a reduction in myocardial excitability, with depression of both pacemaking and conducting tissues in the heart leading to life-threatening arrhythmias and sudden cardiac death.

HK most commonly develops in patients with impaired kidney function such as those with acute kidney injury (AKI) or chronic kidney disease (CKD). This can be due to a variety of reasons including (i) increased K^+ intake from the diet; (ii) alterations in K^+ homeostasis due to insufficient renal clearance of K^+ or pharmacological treatments that interfere with renal K^+ elimination such as renin–angiotensin–aldosterone system inhibitors (RAASi), beta-blockers and K^+-sparing diuretics such as mineralocorticoid receptor antagonists (MRAs) that are commonly prescribed to patients with CKD, diabetes mellitus and heart failure; and (iii) shift of K^+ from the intracellular to the extracellular space seen during haemolysis, tissue injury or metabolic acidosis, for example.

The Kidney Disease: Improving Global Outcomes 2021 blood pressure guidelines [2] recommend targeting lower blood pressure targets in patients with CKD, avoiding RAASi discontinuation where possible and encouraging the use of RAASi in broader groups of patients. HK is implicated in limiting the optimal use of these medications [3] that are recommended for use in patients with heart failure, CKD and diabetes [2, 4, 5], and such limitations of optimal therapy are associated with adverse clinical outcomes and increased mortality [6–9]. The publication of the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease trial results [10] demonstrated that prescribing of the non-steroidal MRA, finerenone, alongside angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-2-receptor blocker (ARB) therapy lowered risk of CKD progression but resulted in an increase in HK incidence.

Table 1. Eligibility criteria for the identification of studies reporting HK prevalence or incidence

Category	Inclusion criteria	Exclusion criteria
Population	• Patients with HK	Animal/*in vitro* studies
Study type	• Non-interventional studies, e.g. observational studies and population surveys	
	• Meta-analyses of relevant study designs	Other study types, e.g. randomized controlled trials, case series or reports
Publication type	• Original research studies	
	• Conference abstracts	
	• SLRs of relevant primary publications (these will be considered relevant at the title/abstract review stage and hand-searched for relevant primary studies, but will be excluded during the full-text review stage)	N/A
Outcomes	• Incidence or prevalence or rate or occurrence or frequency of patients with HK	No reporting of relevant epidemiological outcomes
Date limits	• Conference abstracts will be limited to those published in the last 3 years (i.e. in 2018 or later)	N/A
Language	• Any	N/A
Geographic region	• Any	N/A

Despite the clinical importance of HK, there has remained uncertainty regarding the prevalence and incidence of HK, with many reviews and guidelines acknowledging this when discussing the epidemiology of HK. This is due to the different definitions and thresholds by which studies report HK and the wide range of patient populations described in observational studies. This uncertainty limits awareness of the true burden of disease caused by HK.

As a result of the factors described above, there is a wide variation in the global estimates of the prevalence and incidence of HK. Although studies investigating HK have increased over the last 5 years, there remains no systematic review and meta-analysis of the prevalence and incidence of HK. Therefore, the objective of this systematic literature review (SLR) and meta-analysis is to provide the most comprehensive overview of the epidemiology of HK to date using a range of HK thresholds across different healthcare settings, diseases and continents, to raise awareness and better inform healthcare providers and patients of the burden of HK.

MATERIALS AND METHODS

This SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement with a pre-specified protocol (Supplementary Appendix). The SLR is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO—ID: CRD4202020631).

A comprehensive, systematic search of the literature was conducted using Embase and MEDLINE, which were searched from database inception to 2 February 2021 (the original search was performed from inception to 31 July 2020 and then updated on 4 February 2021) using the Ovid SP platform. The complete search strategy for MEDLINE and Embase is outlined in the Supplementary Appendix.

In addition, conference proceedings (American Society of Nephrology, European Renal Association–European Dialysis and Transplant Association, International Society of Nephrology, European Society for Diabetes, American Heart Association, European Society of Cardiology, National Kidney Foundation and European Society of Cardiology—Heart Failure) were manually searched for the last 3 years (i.e. 2018–20) to identify relevant abstracts.

The eligibility criteria for the SLR are presented in Table 1.

Study selection

Four investigators independently screened abstracts for eligibility against pre-determined inclusion/exclusion criteria using the Rayyan online tool (https://rayyan.qcri.org). Following abstract screening, the full text articles were screened by one author and included if eligibility criteria were met.

Data collection process

Data extraction was undertaken by one investigator, with oversight and quality assurance from the senior author, into a pre-specified data inventory. Relevant information on prevalence and incidence, study characteristics (country, continent and type of study), cohort details, including age of participants, comorbidities and medications, and HK definition/threshold were extracted.

Quality assessment of included studies was assessed by four investigators using the Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies [11] with data collected using a standardized process.

Summary measures

Studies reporting a specific threshold for defining HK were included in the review and the HK definition/threshold was recorded as such. When studies did not provide an HK definition/threshold, then they were included in the review if they reported the proportion of patients within their study with sK^+ concentrations at least >5.0 mmol/L. Where studies reported patients with HK but did not provide a definition/threshold for HK, this was recorded as not reported. Both manuscripts and supplemental material (where available) were searched to identify data.

The principal summary measures extracted were the proportion of patients with HK expressed as a percentage (prevalence) and the incidence rate of HK per 100 person years.

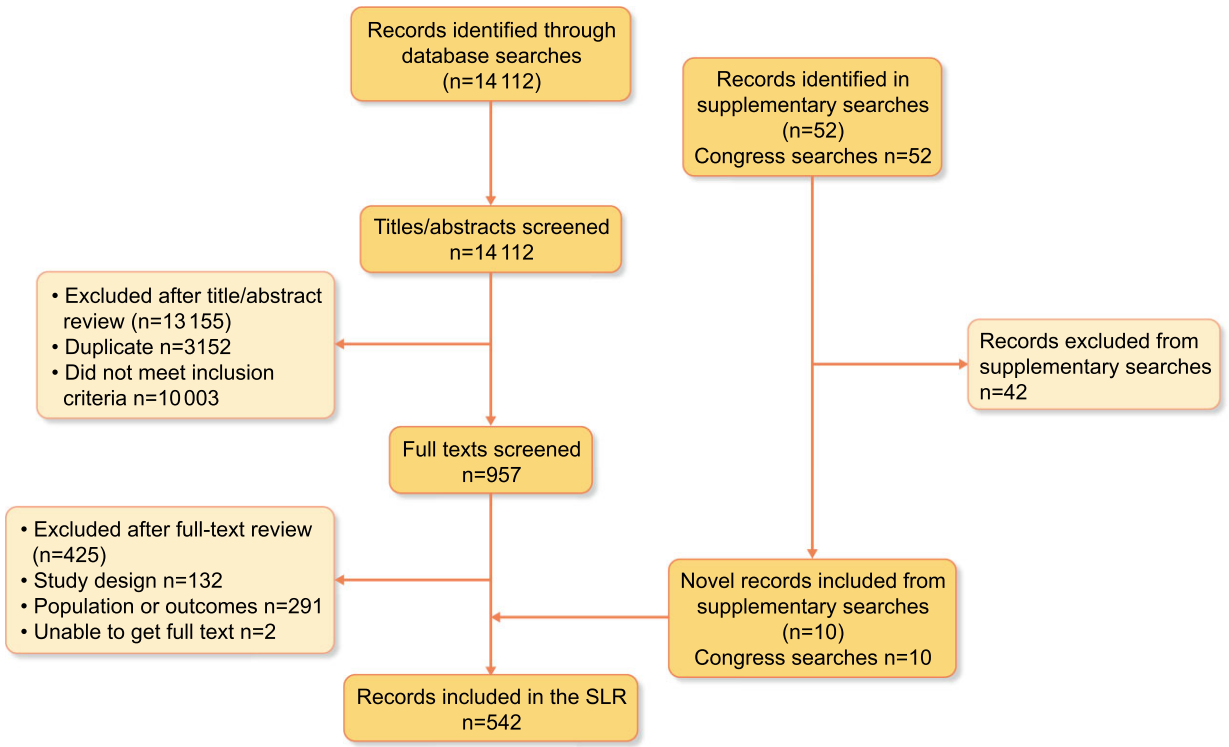


FIGURE 1: PRISMA flow diagram illustrating the study selection process.

Prevalence was calculated using patients with HK as the numerator and total study population as the denominator, multiplied by 100 to give a percentage. Where possible, this method was also used to determine HK prevalence for all subgroups assessed—for example, patients with CKD with HK divided by total patients with CKD for individual studies.

Incidence rate was calculated (if not already reported) by using population number, number of cases of HK and total patient years included in the study and was expressed as a rate per 100 person years. If total patient years were not reported, then the median (or mean) follow-up time was multiplied by the number of patients.

General population was defined as studies reporting patients from an outpatient, registry or primary care setting where the study cohort did not initially specify exact comorbidities nor report patients as taking any specific medications affecting K^+ homeostasis.

Synthesis of results

All prevalence and incidence data, respectively, were log transformed and pooled prevalence and pooled incidence rates [with 95% confidence interval (CI)] calculated using a DerSimonian and Laird random effects meta-analysis [12]. Pooled results were calculated for adult, paediatric and neonatal studies separately. Heterogeneity between studies was assessed using the I^2 statistic.

To ensure a comprehensive summary of results and to help account for potential small study bias, we descriptively assessed study characteristics and created small and large study categories based on the median cohort size ($N = 1250$) across all studies.

Risk of bias across studies

Small study bias was assessed using Egger's linear regression test [13, 14], producing funnel plots and 95% CIs. For all statistical tests, $P < 0.05$ was considered statistically significant.

Additional analyses

Pooled prevalence and pooled incidence rates were calculated for pre-specified adult subgroups both amongst all studies and also differentiated by HK definition/threshold, study setting and geographical area.

Statistical analysis

Data management and analysis was conducted using Stata IC 15.1 (StataCorp, College Station, TX, USA).

RESULTS

A total of 14 112 abstracts and 52 congress abstracts were identified for review, from which 542 articles were included. The PRISMA flow detailing study selection including reasons for exclusion is found in Figure 1 and a complete list of references for the included studies is found in the Supplementary Appendix.

Papers from any language were included—there were 523 (96.5%) articles published in English. The remaining 3.5% consisted of four papers each in Spanish and German, two papers each in French, Portuguese and Japanese, and one paper each in Chinese, Czech, Danish, Italian and Polish.

In total, there were 13 different definitions/thresholds for HK used amongst the included articles, and studies could include more than one definition/threshold. A breakdown

of the number of studies and years of coverage including these definitions/thresholds is provided in Supplementary data, Table S5. The most commonly used definitions/thresholds were sK^+ measurements of >5.0 mmol/L in 203 studies, >5.5 mmol/L in 241 studies and >6.0 mmol/L in 100 studies.

Included papers spanned the years 1976–2021, with 385 (71.2%) studies published on or after 2012. Pooled prevalence and incidence rate were 8.6% and 4.8 per 100 person years in studies published before 2012 versus 6.2% and 2.6 per 100 person years in studies published on or after 2012. A complete breakdown of pooled prevalence and incidence by decade is provided in Supplementary data, Table S6.

Overall prevalence of HK

A total of 527 (97.2%) studies reported prevalence data including any population (adult, neonatal and paediatric) from 63 countries between 1976 and 2021 with individual study size ranging from 18 to 32 910 413 patients. Of these 527 studies, 491 (93.1%) were retrospective and 36 (6.9%) were prospective in design. The overall pooled mean prevalence across all studies and definitions/thresholds of HK was 6.6% (95% CI: 6.1–7.1%; Table 2).

Adult prevalence of HK

A total of 478 (88.0%) studies reported prevalence data in adults (age ≥18 years) from 63 countries between 1976 and 2021 with study size ranging from 18 to 32 910 413 patients. HK prevalence ranged from 0.1 to 73.5%. The pooled mean prevalence of HK, by any definition/threshold, in the general population (as defined in the Methods section) was 1.3% (95% CI: 1.0–1.8%; Table 2).

Prevalence in all adult studies combined was 6.3% (95% CI: 5.8–6.8%; Table 2) and there was evidence of small study bias (Egger's test P = 0.008, funnel plot in Supplementary data, Figure S1). There were 220 studies with fewer than 1250 patients with a prevalence of 13.7% (95% CI: 12.6–14.9%), whilst 258 studies with ≥1250 patients had a prevalence of 4.8% (95% CI: 4.4–5.2%). Comprehensive adult prevalence results for all subgroups are stratified by HK definition/threshold and presented in Table 2.

When stratified by sex, the overall prevalence of HK in males (134 studies) was 6.3% (95% CI: 4.9–8.0) and 5.1% (95% CI: 4.0–6.6) in females (132 studies; Table 2). Additional subgroup HK prevalence stratified by sex is presented in Supplementary data, Table S8 where study numbers permitted.

Paediatric and neonatal prevalence of HK

A total of 26 (4.8%) studies from 19 countries reported prevalence in the general paediatric population between 1987 and 2020. Prevalence ranged from 5.5% (95% CI: 4.1–7.5%) in the outpatient setting to 17.3% (95% CI: 8.3–35.9%) amongst paediatric intensive care patients. The overall pooled mean prevalence of HK in paediatric patients was 14.0% (95% CI: 8.7–22.4%) (Supplementary data, Table S2).

There were 23 (4.2%) studies in the neonatal population from 12 countries between the years 1988 and 2020. All studies were conducted in a neonatal intensive care setting with a pooled mean prevalence of 28.0% (95% CI: 19.7–39.9%) (Supplementary data, Table S2).

Overall incidence of HK

Adult population incidence and subgroups. A total of 65 (12.0%) studies reported incidence data from 16 countries between 1994 and 2020 with study size ranging from 36 to 4 148 468 patients. The pooled mean incidence rate amongst all adult studies was 2.8 (95% CI: 2.3–3.3) cases per 100 person years (Table 2), and there was evidence of small study bias (Egger's test P = 0.05, funnel plot in Supplementary data, Figure S2). Comprehensive adult incidence rate results are stratified by HK definition/threshold in Table 3, and results for all subgroups differentiated by study size are reported in the Supplementary Appendix. There were a lack of data with which to stratify incidence by sex.

Paediatric and neonatal incidence of HK. Only one single-centre paediatric study of solid organ transplant recipients taking calcineurin inhibitors (CNI) reported an incidence rate of HK of 22.0 (95% CI: 15.0–32.4) cases per 100 person years. There were no neonatal studies that reported incidence data.

Additional results. Forest plots of prevalence by K^+ thresholds (Supplementary data, Figure S3) and further results detailing prevalence and incidence stratified by study size (Supplementary data, Tables S2 and S3), decade of study publication (Supplementary data, Table S6) and study setting plus comorbidities (Supplementary data, Table S7) can be found in the Supplementary data.

DISCUSSION

This study provides the first and most comprehensive overview of the epidemiology of HK to date using a range of HK thresholds across different healthcare settings, diseases and continents. In the general and adult population, we report prevalence of HK of 2.3% (95% CI: 1.9–2.8%) and 6.3% (95% CI: 5.8–6.8%), respectively, with an incidence of HK in the adult population of 2.8 (95% CI: 2.3–3.3) cases per 100 person years. We observed that in recent years, there has been a notable increase in the number of studies reporting prevalence and incidence of HK with 385 (71.2%) studies published on or after 2012, although no substantial change in prevalence or incidence, respectively, was reported (8.6% and 4.8 per 100 person years in studies published before 2012 versus 6.2% and 2.6 per 100 person years in studies published on or after 2012).

When evaluating HK by different diseases, the prevalence of HK (by any definition/threshold) was >20% amongst patients receiving dialysis, those with a kidney transplant and patients with AKI, compared with <3% in the general population (Table 2). Prevalence increases to >30% in patients with AKI or a kidney transplant when an sK^+ threshold of ≥5.5 mmol/L is used (Table 2). This is likely to reflect differences in study population, setting and HK definition/threshold used but is also expected as patients with kidney transplants typically have abnormal kidney function. Kidney transplant recipients also often take medications that pre-dispose patients to HK such as CNI for immunosuppression, co-trimoxazole for pneumocystis prophylaxis, and RAASi for blood pressure control and reducing proteinuria. Those with AKI suffer an abrupt loss of kidney function that does not allow for physiological adaptations to control whole body K^+; metabolic acidosis can also occur, which contributes to HK through movement of K^+ from the

Table 2. Pooled mean prevalence for all adult studies, healthcare settings, geographical areas and subgroups stratified by HK definition/threshold

	HK by any definition/threshold	>5.0 mmol/L	≥5.5 mmol/L	≥6.0 mmol/L
All adult studies (*n*)	478	193	221	87
Percentage of population affected (95% CI)	6.3 (5.8–6.8)	8.0 (7.2–8.9)	5.9 (3.5–10.0)	1.0 (0.8–1.4)
I^2-test for heterogeneity	100%	100%	100%	99.9%
General population	39	20	15	5
	1.3 (1.0–1.8)	3.8 (3.2–4.4)	1.3 (0.9–1.9)	0.4 (0.2–0.9)
	100%	100%	100%	100%
Sex				
Male	134	68	64	17
	6.3 (4.9–8.0)	9.0 (7.2–11.2)	6.5 (4.5–9.4)	1.6 (0.6–4.1)
	100%	100%	100%	100%
Female	132	67	64	16
	5.1 (4.0–6.6)	7.4 (5.9–9.1)	5.3 (3.8–7.5)	1.4 (0.5–3.6)
	100%	100%	100%	100%
Study type				
Single centre	304	92	139	52
	9.9 (9.1–10.9)	13.3 (11.8–14.9)	11.1 (9.7–12.8)	5.1 (3.6–7.1)
	99.6%	99.5%	99.6%	99.9%
Multi-centre/registry/database	223	106	92	45
	5.1 (4.6–5.6)	8.5 (7.6–9.6)	5.4 (4.5–6.4)	2.0 (1.5–2.5)
	100%	100%	100%	99.9%
Healthcare setting				
Outpatient/primary care	251	110	105	49
	5.0 (4.5–5.5)	8.7 (7.8–9.8)	5.9 (4.9–7.1)	1.7 (1.3–2.3)
	100%	100%	100%	99.9%
Emergency admissions	49	15	18	7
	7.7 (6.1–9.8)	10.5 (8.1–13.7)	10.4 (7.4–14.7)	2.3 (1.5–3.5)
	99.8%	99.7%	99.8%	99.3%
Hospital inpatients	144	40	65	17
	8.7 (7.8–9.7)	12.5 (10.1–15.5)	8.6 (7.4–9.9)	7.5 (5.4–10.5)
	99.9%	99.9%	99.8%	99.5%
Intensive care[a]	28	14	13	4
	7.1 (5.9–8.6)	7.9 (6.5–9.7)	6.6 (4.1–10.6)	6.5 (4.4–9.4)
	99.7%	99.5%	99.5%	98.7%
Dialysis[b]	48	14	22	11
	20.7 (17.4–24.7)	28.4 (22.6–35.6)	21.2 (19.3–23.4)	12.2 (9.8–15.2)
	100%	100%	99.5%	99.6%
Haemodialysis	38	11	18	10
	23.1 (19.1–28.0)	36.2 (28.4–46.2)	23.4 (21.2–25.7)	12.9 (10.3–16.3)
	100%	100%	99.5%	99.6%
Peritoneal dialysis	9	4	4	2
	11.4 (7.7–16.9)	13.8 (8.1–23.4)	12.3 (5.1–29.6)	4.3 (0.5–35.4)
	99.1%	99.4%	98.8%	98.9%
Continent				
Africa	14	5	3	1
	21.8 (14.4–32.9)	12.1 (6.5–22.5)	36.7 (24.0–55.9)	11.5 (6.2–21.3)
	92.6%	88.0%	81.6%	-
Asia	148	41	54	8
	10.4 (9.2–11.7)	11.6 (9.7–13.9)	11.2 (7.9–15.8)	9.4 (4.2–20.8)
	99.9%	100%	99.9%	99.7%
Australasia	9	3	3	3
	10.1 (8.4–12.0)	23.3 (21.0–25.8)	7.3 (5.2–10.4)	4.6 (3.3–6.5)
	99.5%	97.9%	99.1%	99.2%
Europe	175	79	80	39
	5.9 (5.3–6.6)	7.8 (6.8–9.0)	7.3 (6.0–9.0)	2.8 (1.9–4.2)
	100%	100%	99.9%	99.9%
North America	176	59	72	29
	5.0 (4.4–5.8)	9.3 (7.9–11.0)	5.4 (4.4–6.6)	1.6 (1.2–2.3)
	100%	100%	100%	99.9%
South America	14	4	9	5
	13.4 (10.2–17.5)	22.8 (12.3–42.6)	14.9 (10.7–20.9)	6.2 (3.7–10.5)
	96.7%	98.3%	96.0%	86.7%

Table 2. Continued

	HK by any definition/threshold	>5.0 mmol/L	≥5.5 mmol/L	≥6.0 mmol/L
Global[c]	10	4	5	4
	6.7 (4.1–11.0)	16.5 (3.5–58.0)	8.9 (3.9–20.6)	3.5 (2.7–4.5)
	100%	100%	100%	98.8%
Comorbidity				
CKD non-dialysis[d]	119	57	54	21
	8.5 (7.8–9.3)	14.6 (12.7–16.8)	8.9 (7.6–10.4)	2.5 (1.9–3.3)
	99.9%	99.9%	99.9%	99.7%
End-stage kidney disease[e]	60	17	29	12
	21.5 (18.3–25.3)	33.3 (27.2–40.7)	23.0 (21.0–25.2)	11.6 (9.4–14.3)
	100%	99.9%	99.4%	99.6%
Kidney transplant	18	2	7	4
	21.8 (16.1–29.5)	21.8 (7.0–60.8)	30.8 (20.1–47.2)	12.7 (6.1–26.4)
	98.4%	88.5%	98.2%	92.9%
Diabetes mellitus	64	37	29	11
	5.3 (4.2–6.6)	8.4 (6.3–11.3)	7.2 (4.9–10.8)	1.3 (0.7–2.3)
	99.9%	99.9%	100%	99.5%
Heart failure	104	49	53	23
	6.5 (5.6–7.7)	8.6 (6.7–11.0)	8.0 (6.5–9.8)	3.1 (2.3–4.2)
	99.9%	99.9%	99.7%	99.2%
Hypertension	39	17	13	2
	4.7 (3.9–5.7)	5.1 (3.8–6.8)	3.6 (2.6–4.9)	2.8 (0.5–16.5)
	99.9%	99.9%	99.9%	84.8%
AKI	28	7	11	3
	24.3 (19.3–30.7)	25.7 (16.1–41.2)	31.8 (21.4–47.3)	7.8 (3.5–17.5)
	99.5%	99.7%	98.8%	98.6%
COVID-19 infection	7			
	10.4 (6.8–15.9)			
	74.8%			
Medications				
RAASi[f]	151	53	67	31
	5.8 (5.1–6.6)	9.7 (8.3–11.5)	7.9 (6.6–9.5)	2.5 (1.7–3.7)
	99.9%	99.9%	99.8%	99.7%
ACEi	49	18	25	9
	5.0 (4.0–6.2)	7.9 (5.8–10.8)	7.6 (5.7–10.0)	2.0 (0.8–5.4)
	99.9%	99.9%	99.4%	99.4%
ARB	66	25	27	8
	5.5 (4.1–7.3)	6.7 (4.8–9.3)	8.5 (6.2–11.7)	3.2 (1.1–9.3)
	99.9%	99.9%	99.4%	99.4%
ACEI/ARB plus MRA	9	1	8	2
	14.6 (9.6–22.0)	11.2 (8.7–14.5)	12.8 (7.3–22.2)	21.9 (16.9–28.4)
	95.8%	One study	96.9%	0%
MRA	54	20	22	12
	8.9 (7.2–11.0)	10.1 (7.3–14.1)	11.6 (8.7–15.3)	5.9 (3.9–9.0)
	99.1%	98.6%	96.4%	96.5%
Diuretics	22	13	10	2
	6.6 (5.2–8.3)	8.1 (6.4–10.4)	5.5 (3.0–10.2)	1.3 (0.2–8.2)
	99.5%	99.4%	99.6%	97.3%
CNI	8			
	19.4 (10.8–34.9)			
	97.6%			

[a]Includes patients admitted to coronary care units and high dependency areas.
[b]Only includes studies performed in an outpatient dialysis population and includes patients on both haemodialysis and peritoneal dialysis.
[c]Includes studies performed across different continents.
[d]Includes patients with pre-dialysis CKD 5 (estimated glomerular filtration rate <15 mL/min/1.73 m_2.)
[e]Includes patients from ANY study setting receiving kidney-replacement therapy but NOT pre-dialysis CKD 5 or those with a kidney transplant.
[f]Includes patients taking ACEi, ARB, renin inhibitors and MRAs.
Empty cells are where no data were available. COVID-19, coronavirus disease 2019.

intra- to extra-cellular space. The incidence of HK in these populations followed a similar trend.

For specific classes of medications, we report an increased prevalence of HK in users of RAASi compared to the general population (5.8% versus 2.3%) with no difference between users of ACEi or ARB (5.0% versus 5.5%) (Table 2). Users of MRAs had a higher prevalence of HK at 8.9% (95% CI: 7.2–11.0%), whilst users of dual ACEi/ARB and MRA therapy had a still higher prevalence of 14.6 (9.6–22.0) (Table 2). Patients taking CNIs had the highest HK prevalence [19.4% (95% CI: 10.8–34.9%)] amongst the

Table 3. Pooled mean incidence rate for all adult studies, healthcare settings, geographical areas and subgroups stratified by HK definition/threshold

	HK by any definition/threshold	>5.0 mmol/L	≥5.5 mmol/L	≥6.0 mmol/L
All adult studies (*n*)	65	22	32	19
Incidence—cases per 100-person years (95% CI)	2.7 (2.3–3.3)	8.0 (7.2–8.9)	5.9 (3.5–10.0)	1.0 (0.8–1.4)
I^2 test for heterogeneity	100%	100%	100%	99.9%
General population	5	3	2	2
	0.3 (0.1–0.7)	1.5 (1.1–2.1)	0.6 (0.4–0.9)	(0.1–0.2)
	100%	99.9%	100%	98.3%
Study type				
Single centre	13	5	9	6
	7.7 (4.8–12.3)	13.9 (10.0–19.2)	20.7 (7.6–56.9)	1.5 (0.4–6.3)
	99.7%	99.0%	99.8%	99.6%
Multi-centre/registry/database	52	17	23	13
	2.2 (1.8–2.7)	7.1 (6.3–8.0)	4.0 (2.2–7.3)	0.9 (0.7–1.2)
	100%	100%	100%	100%
Healthcare setting[a]				
Outpatient/primary care	54	21	26	16
	2.3 (2.1–2.7)	8.7 (7.8–9.7)	3.4 (2.9–4.0)	0.9 (0.7–1.1)
	100%	100%	100%	99.9%
Hospital inpatients	4		3	1
	3.7 (1.4–9.6)		5.1 (1.2–22.3)	0.7 (0.6–0.8)
	99.9%		98.7%	One study
Dialysis[c]	5		3	2
	55.3 (25.1–121.7)		153.8 (84.5–279.9)	222.8 (1.6–106.3)
	100%		100%	99.9%
Continent[b]				
Asia	14		2	1
	(0.8–2.9)		3.8 (0.9–15.9)	0.7 (0.6–0.8)
	99.9%		98.6%	One study
Australasia	1	1		1
	5.8 (4.4–7.6)	7.1 (5.2–9.7)		4.7 (3.1–7.0)
	One study	One study		One study
Europe	25	15	19	8
	4.1 (3.4–4.9)	10.2 (8.8–11.9)	4.1 (3.5–4.9)	1.1 (0.8–1.6)
	100%	100%	99.9%	99.9%
North America	24	5	10	8
	2.3 (1.5–3.6)	6.2 (5.3–7.3)	9.1 (3.7–22.2)	0.7 (0.4–1.2)
	100%	99.9%	100%	99.9%
Global[d]	1		1	1
	9.0 (3.8–21.5)		14.0 (13.8–14.3)	5.8 (5.6–6.0)
	100%		One study	One study
Comorbidity				
CKD non-dialysis[e]	27	13	13	7
	4.2 (3.5–4.9)	8.7 (7.7–9.8)	5.9 (4.7–7.4)	2.5 (1.9–3.3)
	100%	99.9%	99.9%	99.7%
End-stage kidney disease[f]	7	1	4	3
	30.0 (14.5–61.9)	8.3 (7.9–8.6)	104.1 (56.3–193.6)	9.8 (2.4–40.4)
	100%	One study	100%	99.9%
Kidney transplant	3	2	1	2
	4.7 (3.0–7.2)	16.9 (12.0–23.6)	22.0 (15.0–32.4)	0.6 (0.5–0.9)
	99.3%	98.9%	One study	76.5%
Diabetes mellitus	14	7	6	4
	(0.7–1.8)	5.0 (2.5–10.1)	3.5 (1.8–7.0)	0.8 (0.4–1.5)
	100%	100%	99.9%	99.7%
Heart failure	19	10	14	8
	4.3 (3.1–6.0)	13.3 (8.6–20.6)	4.2 (2.9–5.9)	1.4 (0.8–2.5)
	100%	100%	99.9%	99.8%

Table 3. Continued

	HK by any definition/threshold	>5.0 mmol/L	≥5.5 mmol/L	≥6.0 mmol/L
Hypertension	6	2	3	1
	3.0 (1.8–5.0)	12.1 (3.0–48.7)	2.1 (1.6–2.8)	0.6 (0.5–0.6)
	100%	93.8%	97.9%	One study
Medications				
RAASi[g]	38	10	17	9
	1.7 (1.4–2.1)	7.6 (6.7–8.7)	3.6 (2.3–5.6)	0.9 (0.5–1.7)
	100%	99.9%	99.9%	99.9%
ACEi	12	2	4	3
	0.7 (0.4–1.1)	12.3 (8.0–18.9)	1.3 (0.7–2.3)	0.4 (0.2–1.1)
	99.9%	99.8%	99.5%	99.0%
ARB	20	4	8	4
	(0.8–2.1)	8.1 (5.2–12.8)	3.2 (1.3–8.1)	0.8 (0.2–2.8)
	99.9%	99.8%	99.8%	99.5%
ACEi/ARB	31	9	15	9
	1.3 (1.1–1.8)	7.3 (6.5–8.1)	3.7 (2.3–5.9)	1.0 (0.5–1.8)
	100%	99.8%	99.9%	99.9%
MRA	9	2	4	1
	4.0 (0.2–71.7)	9.9 (2.9–33.6)	4.0 (0.9–18.0)	0.3 (0.2–0.4
	99.6%	99.8%	99.4%	One study
Diuretics	3		3	
	4.0 (0.2–71.7)		4.0 (0.2–71.7)	
	99.9%		99.9%	
CNI	4		4	
	7.1 (0.8–66.2)		7.1 (0.8–66.2)	
	99.7%		99.7%	

[a]There were no emergency or intensive care studies reporting incidence.
[b]There were no studies reporting incidence in Africa or South America.
[c]Only includes studies performed in an outpatient dialysis population. There were no studies reporting incidence of HK in peritoneal dialysis patients, results are specific to patients on haemodialysis.
[d]Includes studies performed across different continents.
[e]Includes patients with pre-dialysis CKD 5 (estimated glomerular filtration rate <15 mL/min/1.73 m_2.)
[f]Includes patients receiving kidney-replacement therapy from ANY study setting but NOT pre-dialysis CKD 5 or those with a kidney transplant.
[g]Includes patients taking ACEi, ARB, renin inhibitors and MRAs.
Empty cells are where no data were available.

medications assessed in this review (Table 2). This is likely related to both the patient groups who take CNIs, such as those with kidney transplants, and also to direct class effects of CNIs, which can lower glomerular filtration rate, impair renin release and directly interfere with secretion of K^+ in the kidneys collecting duct [15].

The observed increasing prevalence and incidence from primary care to secondary and tertiary care is not surprising since those in hospital are likely to be sicker and will also undergo increased monitoring of bloods. HK was highest in the dialysis population and those with impaired kidney function. This is primarily due to impaired removal of K^+ via the kidney but may also reflect increased K^+ testing that patients with impaired kidney function undergo [1].

The prevalence of HK reported in observational studies across different continents varies, with the highest prevalence reported in African studies [21.8% (95% CI: 14.4–32.9%)] and lowest in studies from North America [5.0% (95% CI: 4.4–5.8%)] (Table 2). It should be noted, however, that whilst 67% of North American studies examined HK amongst outpatients or those in primary care (Supplementary data, Table S4), African studies were smaller, and focussed on patients at increased risk of HK [primarily those with either CKD or AKI in conjunction with infectious diseases such as Ebola, malaria and human immunodeficiency virus (HIV)]. African populations carry the heaviest burden of HIV infection, with 25.7 million people living with HIV in the WHO Africa Region in 2018 (https://www.afro.who.int/health-topics/hivaids). A broad spectrum of kidney diseases is seen in patients with HIV infection and high prevalence of HK might therefore be expected because of HIV-related kidney disease and the widespread use in these patients of medications (such as trimethoprim), which impair renal K^+ excretion. There are however a paucity of studies from Africa exploring HK in these specific patient populations and additional data would be invaluable to better quantify the burden of HK in Africa. The prevalence of HK in Asian studies was approximately double that in European and North American studies (10.1% versus 5.9% and 5.0%, respectively) (Table 2), though it should be noted that there was a higher proportion of studies of hospital inpatients in Asia (28% versus 13% and 18%, respectively) (Supplementary data, Table S4).

Strengths

This systematic review offers a comprehensive overview and meta-analysis of the epidemiology of HK from observational studies both within the general population and specific healthcare settings covering all continents, languages, key subgroups of comorbidities and medication classes. Our review

has broad inclusivity of different definitions/thresholds of HK and included multiple bibliographical databases and congress proceedings to capture as many studies as possible, reducing the risk of excluding relevant articles. Other strengths include that search terms were not limited to the abstracts, and full text review included supplemental material. There were no language criteria applied for searches or data extraction in order to limit English-language bias. The outcomes extracted are objective and do not require reviewer judgement, which limits bias in study selection and data extraction. The methodology used in this review is consistent with other published analyses of prevalence data [16], follows PRISMA guidelines and is registered on the PROSPERO registry.

Limitations

Although there are major strengths of this review, there are limitations to acknowledge. The prevalence and incidence data that contribute to the review and meta-analysis include, and are more reflective of, populations at risk of HK, so careful consideration and context are needed when utilizing these results. Additionally, there was heterogeneity in prevalence reporting between studies, with some reporting point prevalence, others period prevalence and in some studies it was not clear which method had been used. Data on blood sampling methods, storage and processing were unavailable and therefore we were unable to comment on the impact this might have, but acknowledge this could contribute to differences in results observed. Given the broad inclusion criteria, there is potential for duplication of underlying populations and double counting of patients due to the non-exclusivity of patient populations. For example, we acknowledge that studies specific to CKD will include patients who also have heart failure, diabetes, etc., and similarly with medications it is not clear in many studies whether multiple drug use occurred. The broad inclusion also includes different healthcare settings, which contribute to varying ranges of prevalence and incidence and may reflect variations in patient management and monitoring. The studies included in this review also have limitations with respect to the design (e.g. cross-sectional or longitudinal) and underlying real-world data, which include study specific inclusion/exclusion criteria applied and the populations from which they derive are subject to confounding/distortion from both controlled and residual factors, e.g. diet, lack data granularity, may under- or overestimate or misclassify patients and may be subject to publication bias. Also, although we split estimates based on median study size, smaller studies are likely to drive up estimates and may also reflect sicker populations. Lastly, in a very small number of studies, contact with authors to identify and retrieve omitted data or to answer potential queries was not possible and we were also unable to access the full text for two articles.

Conclusions

This novel review provides a comprehensive and valuable resource on the prevalence and incidence of HK for healthcare professionals and health policymakers when considering the burden of HK for both patients and healthcare systems. This highlights the need for awareness of this common complication and for careful management and prescribing of medications that affect K^+ homeostasis.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: T.H., G.J., M.R.D. and M.-Y.C.; substantial contributions to analysis and interpretation of the data: T.H., G.J., M.R.D., M.-Y.C., R.P.-F. and C.P.; drafting the article or revising it critically for important intellectual content: T.H., G.J., M.R.D., M.-Y.C., R.P.-F. and C.P.; final approval of the version of the article to be published: T.H., G.J., M.R.D., M.-Y.C., R.P.-F. and C.P.

CONFLICT OF INTEREST STATEMENT

T.H. is a PhD student supported by the Cambridge Experimental Medicine Initiative (EMI) programme and receives research funding from both the NIHR Cambridge BRC and AstraZeneca. G.J. is an employee and stockholder of AstraZeneca. C.P. reports Advisory Board membership for AstraZeneca, Vifor, Eli Lilly and Boehringer Ingelheim, as well as speaker fees for Novartis, Janssen Cilag, Otsuka, AstraZeneca and Vifor. R.P.-F. is a consultant for Akebia, AstraZeneca, Novo Nordisk and Fresenius, and receives research grants from Fresenius. M.R.D. and M.-Y.C. have no conflicts of interest to report.

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Supplementary Appendix

Figures and Tables

Figure 1: Funnel plot to assess publication and small study bias amongst prevalence studies

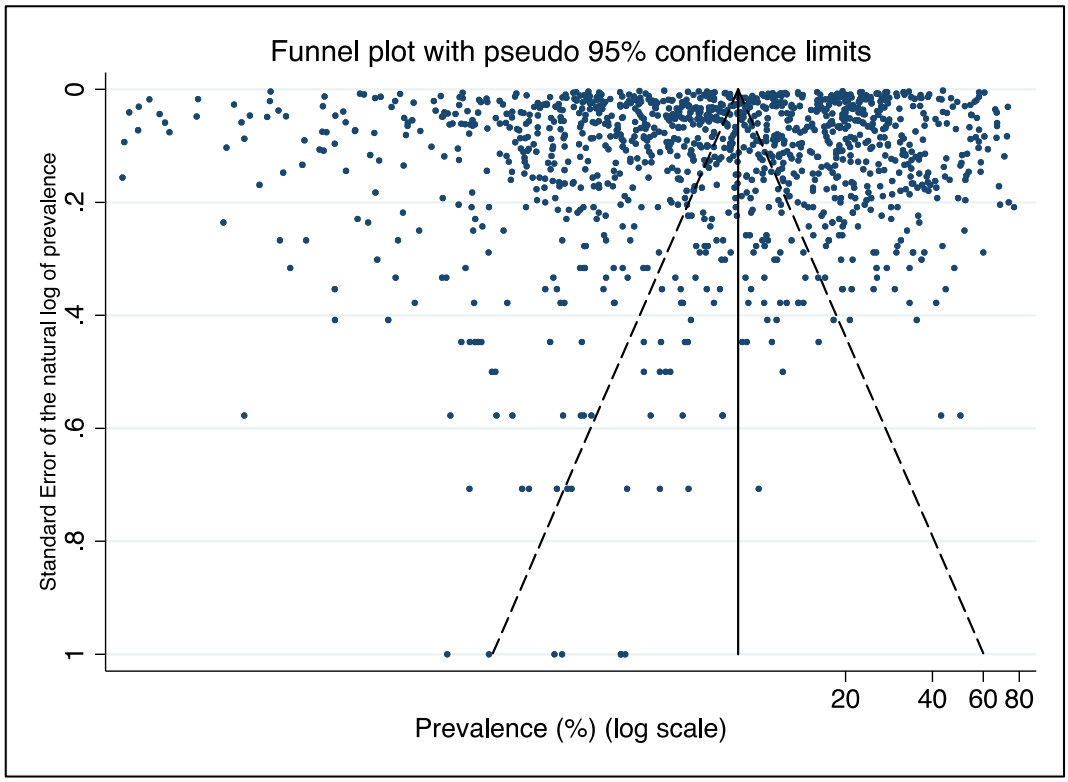


Figure 2: Funnel plot to assess publication and small study bias amongst incidence studies

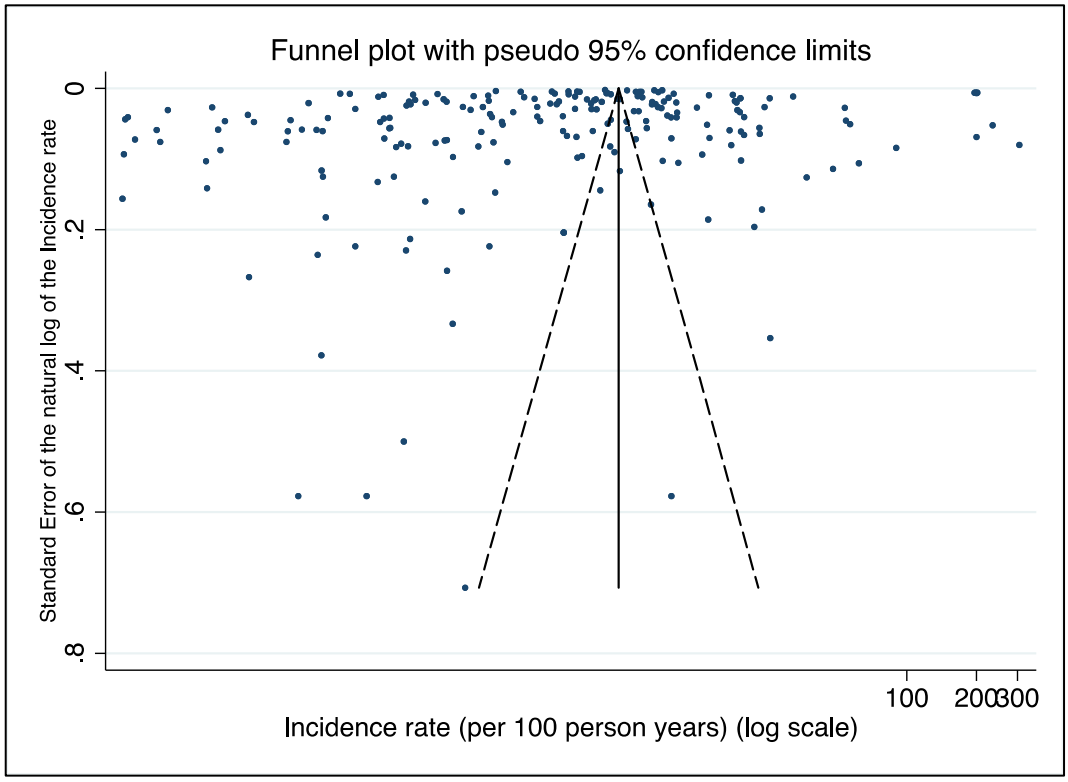
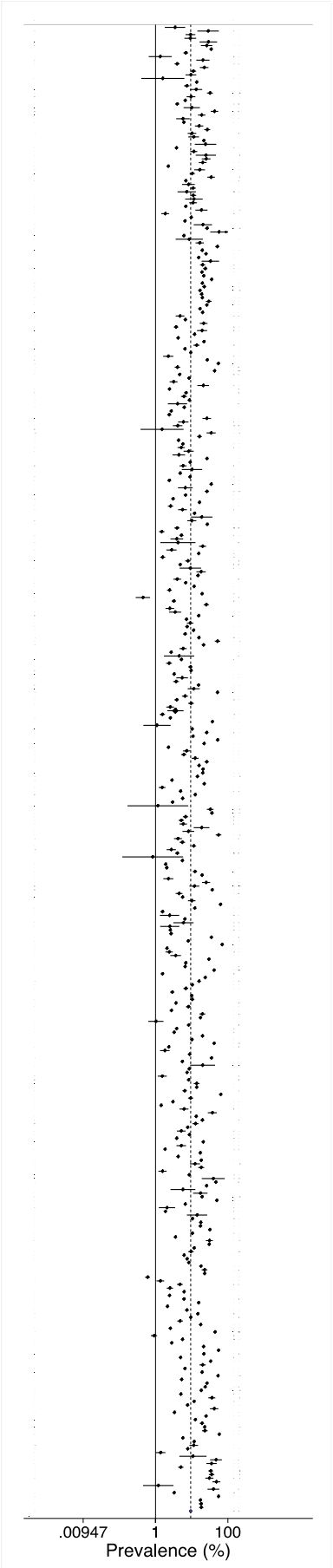
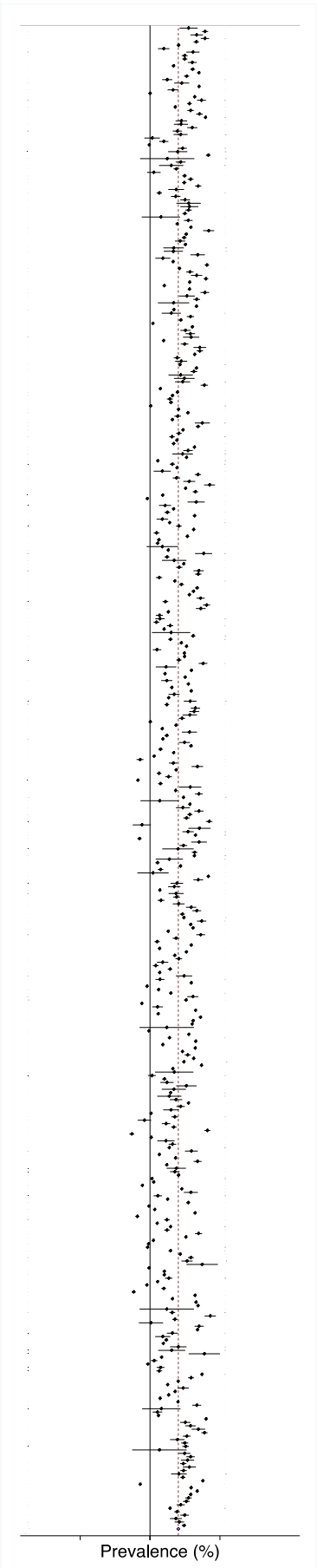


Figure 3: Forest plots displaying pooled mean prevalence for all studies by HK definition (left to right : >5.0mmol/L, ≥5.5 mmol/L, ≥ 6.0 mmol/L)





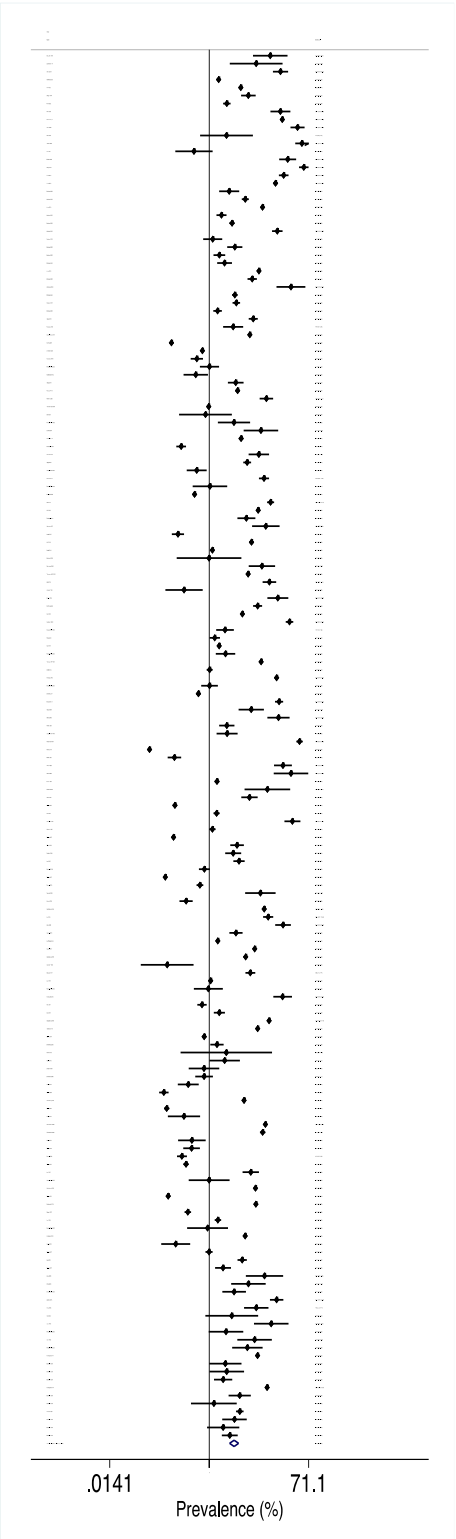


Table 1. Search terms for MEDLINE and Embase (to be searched simultaneously via the Ovid SP platform)

Domain	#	Search terms
Hyperkalaemia	1	exp Hyperkalemia/
	2	hyperkal*
	3	Hyperpotass*
	4	((Raised or elevated or increased or high) adj (blood or serum or plasma) adj (potassium))
	5	Exp potassium blood level/
	6	or/1-6
Epidemiology	7	epidemiological data/ or epidemiology/ or epidemiologic studies/ or epidemiolog*
	8	incidence/ or inciden*
	9	prevalence/ or prevalen*
	10	Rate.ti,ab.
	11	Occurrence.ti,ab.
	12	frequency.ti,ab.
	13	Exp case control studies/ or case control.tw or (Case control adj (study or studies)).tw.
	14	Exp cohort studies/ or (cohort adj (study or studies)).tw.or Cohort analy$.tw. or cohort analysis/
	15	(Follow up adj (study or studies)).tw.
	16	(observational adj (study or studies)).tw.
	17	Retrospective study/ or restrospective.tw.
	18	Longitudinal study/ or Longitudinal.tw.
	19	Prospective study/
	20	Cross-sectional studies/ or Cross sectional.tw. or (cross sectional adj (study or studies)).tw.
	21	or/7-20
Exclusion terms	22	(conference abstract or conference review).pt.
	23	limit 22 to yr="1974-2017"
	24	exp animals/ not exp humans/
	25	Or/22-24
Total	26	6 and 21
	27	26 not 25

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Version(R) 1946 to Feb 2, 2021, Embase 1974 to 2021 Feb 2

Table 2: Summary of the pooled mean prevalence for all combined studies, ages, co-morbidities, study settings, medications and continents and also stratified by study size

	All studies combined	Studies with N <1250	Studies with N ≥1250
Overall			
Percentage of population affected (95% confidence intervals) I^2 statistic for heterogeneity	6.6 (6.1-7.1) I^2 – 100% Egger's test: p = 0.008	14.6 (13.5-15.7) I^2 – 96.1%	4.8 (4.4-5.2) I^2 – 100%
Age			
All Adults	6.3 (5.8-6.8) I^2 – 100%	13.7 (12.6-14.9) I^2 – 96.3%	4.8 (4.4-5.2) I^2 – 100%
Adults >65years	3.7 (2.7-5.2) I^2 – 100%	10.4 (2.9-37.0) I^2 – 98.3%	3.4 (2.4-4.9) I^2 – 100%
Paediatric	14.0 (8.7-22.4) I^2 – 96.7	15.9 (12.0-20.9) I^2 – 88.3%	4.6 (0.1-55.3) I^2 – 99.6%
Neonatal	28.0 (19.7-39.9) I^2 – 96.4%	33.1 (26.4-41.4) I^2 – 87.8%	5.3 (2.3-12.4) I^2 – 80.9%
K+ Severity			
>5.0 mmol/L	9.6 (8.7-10.6) I^2 – 100%	16.0 (14.2-18.1) I^2 – 95%	8.4 (7.5-9.3) I^2 – 100%
>5.5 mmol/L	7.6 (6.8-8.6) I^2 – 100%	15.5 (13.7-17.5) I^2 – 96.2%	5.3 (4.5-6.1) I^2 – 100%
>6.0 mmol/L	2.9 (2.4-3.5) I^2 – 99.9%	8.3 (6.1-11.2) I^2 – 95.9%	1.9 (1.5-2.4) I^2 – 99.9%
ICD Code Only	3.4 (2.3-4.8) I^2 – 100%	8.5 (6.8-10.6) 1 study	3.3 (2.3-4.8) I^2 – 100%
Co-Morbidity			
CKD-ND	8.5 (7.8-9.3) I^2 – 99.9%	13.6 (11.8-15.6) I^2 – 96.0%	7.5 (6.7-8.3) I^2 – 99.9
>5.0 mmol/L	14.6 (12.7-16.8) I^2 – 99.9%	26.1 (22.8-29.8) I^2 – 90.1%	12.7 (10.9-14.9) I^2 – 100%
>5.5 mmol/L	8.9 (7.6-10.4) I^2 – 99.9%	13.1 (10.6-16.1) I^2 – 96.1%	7.5 (6.2-9.1) I^2 – 99.9%
>6.0 mmol/L	2.5 (1.9 – 3.3) I^2 – 99.7%	2.3 (1.4-3.9) I^2 – 82.4%	2.5 (1.9-3.4) I^2 – 99.8%
ESKD	21.5 (18.3-25.3) I^2 – 100%	29.6 (24.5-35.8) I^2 – 96.1%	16.3 (13.1-20.4) I^2 – 100%
>5.0 mmol/L	33.3 (27.2-40.7) I^2 -99.9%	30.6 (21.2-44.3) I^2 – 95.5%	35.0 (27.1-45.2) I^2 – 100%
>5.5 mmol/L	23.0 (21.0-25.2) I^2 – 99.4%	28.2 (21.1-37.8) I^2 – 96.1%	18.8 (16.8-21.1) I^2 – 99.7%
>6.0 mmol/L	11.6 (9.4-14.3) I^2 – 99.6%	19.6 (11.7-32.9) I^2 – 94.2%	7.8 (6.0-10.1) I^2 – 99.7%
Kidney Transplant	21.8 (16.1-29.5) I^2 – 98.4%	24.4 (18.8-31.7) I^2 – 90.3%	11.3 (5.7-22.3) I^2 – 99.7%
>5.0 mmol/L	21.8 (7.0-60.8) I^2 -88.5%	21.8 (7.0-67.9) I^2 – 88.5%	No studies
>5.5 mmol/L	30.8 (20.1-47.2) I^2 – 98.2%	34.3 (25.5-46.2) I^2 – 89.4%	16.0 (15.4-16.7) 1 study
>6.0 mmol/L	12.7 (6.1-26.4)	16.8 (8.3-34.0)	8.0 (7.6-8.5)

	I^2 – 92.9%	I^2 – 74.4%	1 study
Diabetes	5.3 (4.2-6.6) I^2 – 99.9%	15.0 (11.5-19.7) I^2 – 90.5%	4.2 (3.3-5.4) I^2 – 99.9%
>5.0 mmol/L	8.4 (6.3-11.3) I^2 – 99.9%	9.2 (5.5-15.4) I^2 –	8.3 (5.9-11.7) I^2 – 99.9%
>5.5 mmol/L	7.2 (4.9-10.8) I^2 – 100%	24.3 (19.5-30.1) I^2 – 74.3%	5.0 (3.2-7.8) I^2 – 100%
>6.0 mmol/L	1.3 (0.7-2.3) I^2 – 99.5%	No studies	1.3 (0.7-2.3) I^2 – 99.5%
Heart Failure	6.5 (5.6-7.7) I^2 – 99.9%	10.0 (8.3-12.1) I^2 – 91.5%	5.6 (4.6-6.8) I^2 – 99.9%
>5.0 mmol/L	8.6 (6.7-11.0) I^2 – 99.9%	13.6 (9.0-20.5) I^2 – 92.9%	8.0 (6.1-10.5) I^2 – 99.9%
>5.5 mmol/L	8.0 (6.5-9.8) I^2 – 99.7%	11.1 (8.6-14.3) I^2 – 89.3%	6.6 (5.0-8.6) I^2 – 99.8%
>6.0 mmol/L	3.1 (2.3-4.2) I^2 – 99.2%	6.1 (4.1-9.1) I^2 – 82.4%	2.4 (1.7-3.4) I^2 – 99.5%
Hypertension	4.7 (3.9-5.7) I^2 – 99.9%	9.4 (5.9-14.9) I^2 – 92.3%	4.2 (3.5-5.2) I^2 – 99.9%
>5.0 mmol/L	5.1 (3.8-6.8) I^2 – 99.9%	9.1 (5.7-14.6) I^2 – 80.3%	4.7 (3.5-6.3) I^2 – 99.9%
>5.5 mmol/L	3.6 (2.6-4.9) I^2 – 99.9%	11.5 (6.2-21.2) I^2 – 92.3%	2.5 (1.8-3.7) I^2 – 99.9%
>6.0 mmol/L	2.8 (0.5-16.5) I^2 – 84.8%	1.0 (0.3-4.0) 1 study	6.1 (5.5-6.8) 1 study
AKI	24.3 (19.3-30.7) I^2 – 99.5%	32.2 (26.3-39.4) I^2 – 91.3%	16.9 (11.7-24.2 I^2 – 99.8%
>5.0 mmol/L	25.7 (16.1 – 41.2) I^2 – 99.7%	33.6 (19.5-58.1) I^2 – 83.4%	22.1 (12.2-39.9) I^2 – 99.8%
>5.5 mmol/L	31.8 (21.4-47.3) I^2 – 98.8%	38.0 (30.5-47.4) I^2 – 85.4%	13.0 (4.5-35.5) I^2 – 99.8%
>6.0 mmol/L	7.8 (3.5-17.5) I^2 – 98.6%	No studies	7.8 (3.5-17.5) I^2 – 98.6%
COVID-19	10.4 (6.8-15.9) I^2 – 74.8%	10.4 (6.8-15.9) I^2 – 74.8%	No data
Healthcare Setting			
Outpatient/Primary Care	5.0 (4.5-5.5) I^2 – 100%	12.7 (11.4-14.2) I^2 – 95.6%	4.0 (3.5-4.4) I^2 – 100%
>5.0 mmol/L	8.7 (7.8-9.8) I^2 – 100%	18.2 (15.7-21.0) I^2 – 94.9%	7.6 (6.7-8.6) I^2 – 100%
>5.5 mmol/L	5.9 (4.9-7.1) I^2 – 100%	14.1 (12.0-16.5) I^2 – 95.3%	4.2 (3.4-5.3) I^2 – 100%
>6.0 mmol/L	1.7 (1.3-2.3) I^2 – 99.9%	3.6 (2.4-5.5) I^2 – 92.1%	1.4 (1.1-2.0) I^2 – 99.9%
Emergency Admissions	7.7 (6.1-9.6) I^2 – 99.8%	16.0 (12.4-20.7) I^2 – 96.7%	5.6 (4.3-7.2) I^2 – 99.8%
>5.0 mmol/L	10.5 (8.1-13.7) I^2 – 99.7%	10.9 (6.7-17.6) I^2 – 95.4%	10.4 (7.6-14.2) I^2 – 99.8%
>5.5 mmol/L	10.4 (7.4-14.7) I^2 – 99.8%	24.7 (16.9-36.1) I^2 – 96.4%	6.8 (4.7-9.9) I^2 – 99.8%
>6.0 mmol/L	2.3 (1.5-3.5) I^2 – 99.3%	10.2 (5.1-20.4) I^2 – 83.8%	1.7 (1.1-2.7) I^2 – 99.4%
Hospital Inpatients	8.7 (7.8-9.7) I^2 – 99.9%	11.7 (9.9-13.9) I^2 – 95.1%	6.9 (5.9-8.0) I^2 – 99.9%
>5.0 mmol/L	12.5 (10.1-15.5)	13.5 (10.4-17.4)	11.8 (8.7-15.9)

	I^2 – 99.9%	I^2 – 91.4%	I^2 – 100%
>5.5 mmol/L	8.6 (7.4-9.9) I^2 – 99.8%	11.8 (9.1-15.4) I^2 – 95.3%	6.9 (5.7-8.3) I^2 – 99.9%
>6.0 mmol/L	7.5 (5.4-10.5) I^2 – 99.5%	11.6 (6.8-19.9) I^2 – 90.4%	5.0 (3.2-8.0) I^2 – 99.7%
Intensive Care*	7.1 (5.9-8.6) I^2 – 99.7%	15.2 (10.3-22.4) I^2 – 96.5%	5.5 (4.5-6.8) I^2 – 99.7%
>5.0 mmol/L	7.9 (6.5-9.7) I^2 – 99.5%	8.4 (3.7-19.0) I^2 – 96.6%	7.8 (6.3-9.6) I^2 – 99.6%
>5.5 mmol/L	6.6 (4.1-10.6) I^2 – 99.5%	18.3 (11.6-28.8) I^2 – 95.6%	2.5 (1.4-4.7) I^2 – 99.6%
>6.0 mmol/L	6.5 (4.4-9.4) I^2 – 98.7%	No studies	6.5 (4.4-9.4) I^2 – 98.7%
Dialysis⁺	20.7 (17.4-24.7) I^2 – 100%	28.4 (22.4-33.6) I^2 – 96.0%	15.9 (12.4-20.3) I^2 – 100%
>5.0 mmol/L	28.4 (22.6 – 35.6) I^2 - 100%	30.6 (21.2-44.3) I^2 – 95.5%	26.5 (19.4-36.3) I^2 – 100%
>5.5 mmol/L	21.2 (19.3-23.4) I^2 - 99.5%	26.2 (18.9-36.4) I^2 – 96.0%	17.3 (15.3-19.6) I^2 – 99.7%
>6.0 mmol/L	12.2 (9.8-15.2) I^2 - 99.6%	19.6 (11.7-32.9) I^2 – 94.2%	8.0 (6.0-10.6) I^2 – 99.8%
Medication Use			
RAASi#	5.8 (5.1-6.6) I^2 – 99.9%	11.4 (9.8-13.3) I^2 – 94.5%	4.4 (3.8-5.1) I^2 – 100%
>5.0 mmol/L	9.7 (8.3-11.5) I^2 – 99.9%	18.8 (15.2-23.4) I^2 – 93.2%	7.8 (6.4-9.4) I^2 – 100%
>5.5 mmol/L	7.9 (6.6-9.5) I^2 – 99.8%	11.9 (9.7-14.7) I^2 – 93.9%	6.2 (4.9-7.8) I^2 – 99.9%
>6.0 mmol/L	2.5 (1.7-3.7) I^2 – 99.7%	5.4 (3.3-8.6) I^2 – 92.8%	1.7 (1.1-2.8) I^2 – 99.8%
ACEi	5.0 (4.0-6.2) I^2 – 99.9%	12.3 (9.5-15.8) I^2 – 94.6%	3.4 (2.6-4.4) I^2 – 99.9%
>5.0 mmol/L	7.9 (5.8-10.8) I^2 – 99.9%	17.8 (13.0-24.4) I^2 – 92.3%	5.2 (3.6-7.6) I^2 – 99.9%
>5.5 mmol/L	7.6 (5.7-10.0) I^2 – 99.4%	13.7 (9.9-18.9) I^2 – 89.7%	6.0 (4.3-8.2) I^2 – 99.5%
>6.0 mmol/L	2.0 (0.8-5.4) I^2 – 99.4%	6.9 (3.0-16.3) I^2 – 95.5%	0.6 (0.2-1.8) I^2 – 99.4%
ARB	5.5 (4.1-7.3) I^2 – 99.9%	11.5 (8.5-15.6) I^2 – 96.2%	4.1 (2.9-5.7) I^2 – 99.9%
>5.0 mmol/L	6.7 (4.8-9.3) I^2 – 99.9%	14.8 (8.7-25.0) I^2 – 94.4%	5.3 (3.6-7.8) I^2 – 99.9%
>5.5 mmol/L	8.5 (6.2-11.7) I^2 – 99.4%	10.8 (6.9-16.9) I^2 – 96.3%	7.5 (5.1-11.1) I^2 – 99.5%
>6.0 mmol/L	3.2 (1.1-9.3) I^2 – 99.4%	14.1 (4.2-47.5) I^2 – 96.7%	1.2 (0.3-5.0) I^2 – 99.6%
ACEi/ARB	5.4 (4.7-6.2) I^2 – 99.9%	11.4 (9.6-13.6) I^2 – 95.1%	4.0 (3.4-4.8) I^2 – 100%
>5.0 mmol/L	9.7 (8.0-11.6) I^2 – 99.9%	19.7 (15.9-24.5) I^2 – 91.9%	7.8 (6.3-10.0) I^2 – 100%
>5.5 mmol/L	7.4 (6.1-9.1) I^2 – 99.8%	11.8 (9.2-15.0) I^2 – 95.1%	5.8 (4.5-7.5) I^2 – 99.9%
>6.0 mmol/L	2.0 (1.3-3.3) I^2 – 99.8%	5.0 (2.7-9.4) I^2 – 94.5%	1.3 (0.7-2.4) I^2 – 99.9%
MRA	8.9 (7.2-11.0)	13.2 (10.2-17.1)	6.5 (4.8-8.7)

	I^2 – 99.1%	I^2 – 90.6%	I^2 – 99.5%
>5.0 mmol/L	10.1 (7.3-14.1) I^2 – 98.6%	15.9 (8.5-29.6) I^2 – 95.5%	7.6 (5.1-11.3) I^2 – 98.9%
>5.5 mmol/L	11.6 (8.7-15.3) I^2 – 96.4%	14.5 (10.6-19.9) I^2 – 85.0%	9.0 (6.0-13.5) I^2 – 98.1%
>6.0 mmol/L	5.9 (3.9-9.0) I^2 – 96.5%	11.3 (6.8-18.9) I^2 – 85.4%	3.6 (2.0-6.3) I^2 – 97.8%
Diuretics	6.6 (5.2-8.3) I^2 – 99.5%	18.4 (10.2-33.1) I^2 – 95.9%	5.7 (4.4-7.3) I^2 – 99.5%
>5.0 mmol/L	8.1 (6.4-10.4) I^2 – 99.4%	37.7 (30.2-47.1) 1 study	7.6 (5.9-9.7) I^2 – 99.4%
>5.5 mmol/L	5.5 (3.0-10.2) I^2 – 99.6%	22.1 (17.0-28.7) I^2 – 46.2%	3.7 (1.8-7.4) I^2 – 99.7%
>6.0 mmol/L	1.3 (0.2-8.2) I^2 – 97.3%	No Studies	1.3 (0.2-8.2) I^2 – 97.3%
CNIs	11.7 (6.5-20.8) I^2 – 84.9%	14.8 (11.0-19.8) I^2 – 0.0%	5.2 (3.9-6.9) 1 study
>5.0 mmol/L	5.2 (3.9-6.9) 1 study	No studies	5.2 (3.9-6.9) 1 study
>5.5 mmol/L	No studies	No studies	No studies
>6.0 mmol/L	No studies	No studies	No studies
Continent			
Africa	21.8 (14.4-32.9) I^2 – 92.6%	20.9 (13.5-32.5) I^2 – 93.1%	35.7 (23.0-55.3) I^2 – 1 study
>5.0 mmol/L	12.1 (6.5-22.5) I^2 – 88.0%	12.1 (6.5-22.5) I^2 – 88.0%	No studies
>5.5 mmol/L	36.7 (24.0-55.9) I^2 – 81.6%	36.7 (24.0-56.0) I^2 – 81.6%	No studies
>6.0 mmol/L	11.5 (6.2-21.3) I^2 – 0.0%	11.5 (6.2-21.3) I^2 – 0.0%	No studies
Asia	10.4 (9.2-11.7) I^2 – 99.9%	17.0 (14.8-19.6) I^2 – 96.2%	6.9 (5.9-8.2) I^2 – 100%
>5.0 mmol/L	11.6 (9.7-13.9) I^2 – 100%	16.6 (13.6-20.2) I^2 – 91.7%	7.8 (6.0-10.2) I^2 – 100%
>5.5 mmol/L	11.2 (7.9-15.8) I^2 – 99.9%	16.4 (12.9-20.9) I^2 – 96.8%	8.9 (5.7-13.9) I^2 – 99.9%
>6.0 mmol/L	9.4 (4.2-20.8) I^2 – 99.7%	21.1 (11.2-39.6) I^2 – 96.6%	2.8 (0.8-9.7) I^2 – 99.9%
Australasia	10.1 (8.4-12.0) I^2 – 99.5%	25.3 (20.4-31.5) I^2 – 53.8	8.8 (7.3-10.7) I^2 – 99.6%
>5.0 mmol/L	23.3 (21.0-25.8) I^2 – 97.9%	24.7 (15.5-39.3) I^2 – 63.4%	23.2 (20.8-25.9) I^2 – 98.1%
>5.5 mmol/L	7.3 (5.2-10.4) I^2 – 99.1%	43.3 (25.2-74.6) 1 study	6.6 (4.6-9.4) I^2 – 99.2%
>6.0 mmol/L	4.6 (3.3-6.5) I^2 – 99.2%	33.3 (17.9-62.0) 1 study	4.2 (2.9-5.9) I^2 – 99.3%
Europe	5.9 (5.3-6.6) I^2 – 100%	14.5 (12.7-16.6) I^2 – 95.3%	4.4 (3.8-5.0) I^2 – 100%
>5.0 mmol/L	7.8 (6.8-9.0) I^2 – 100%	§3.9 (10.6-18.3) I^2 – 96.4%	7.1 (6.1-8.2) I^2 – 100%
>5.5 mmol/L	7.3 (6.0-9.0) I^2 – 99.9%	16.8 (13.9-20.3) I^2 – 94.7%	4.5 (3.5-5.8) I^2 – 100%
>6.0 mmol/L	2.8 (1.9-4.2) I^2 – 99.9%	8.4 (5.2-13.5) I^2 – 95.0%	1.9 (1.2-3.0) I^2 – 99.9%
North America	5.0 (4.4-5.8)	11.3 (9.7-13.3)	4.1 (3.5-4.7)

	I^2 – 100%	I^2 – 96.2%	I^2 – 100%
>5.0 mmol/L	9.3 (7.9-11.0) I^2 – 100%	14.1 (11.0-18.0) I^2 – 95.8%	8.7 (7.3-10.4) I^2 – 100%
>5.5 mmol/L	5.4 (4.4-6.6) I^2 – 100%	12.2 (9.4-15.7) I^2 – 96.3%	4.0 (3.2-5.1) I^2 – 100%
>6.0 mmol/L	1.6 (1.2-2.3) I^2 – 99.9%	4.7 (2.4-9.4) I^2 – 96.7%	1.3 (0.9-1.8) I^2 – 99.9%
South America	13.4 (10.2-17.5) I^2 – 96.7%	13.9 (10.9-17.9) I^2 – 95.6%	5.1 (4.3-6.1) 1 study
>5.0 mmol/L	22.8 (12.3-42.6) I^2 – 98.3%	32.9 (25.0-43.3) I^2 – 87.8%	5.1 (4.3-6.1) 1 study
>5.5 mmol/L	14.9 (10.7-20.9) I^2 – 96.0%	14.9 (10.7-20.9) I^2 – 96.0%	No studies
>6.0 mmol/L	6.2 (3.7-10.5) I^2 – 86.7%	6.2 (3.7-10.5) I^2 – 86.7%	No studies
Global^	6.7 (4.1-11.0) I^2 – 100%	18.9 (17.3-20.8) I^2 – 0.0%	6.2 (3.7=10.4) I^2 – 100%
>5.0 mmol/L	16.5 (3.5-58.0) I^2 – 100%	18.9 (17.3-20.8) I^2 – 0.0%	15.1 (2.0-58.6) I^2 – 100%
>5.5 mmol/L	8.9 (3.9-20.6) I^2 – 100%	No studies	8.9 (3.9-20.6) I^2 – 100%
>6.0 mmol/L	3.5 (2.7-4.5) I^2 – 98.8%	No studies	3.5 (2.7-4.5) I^2 – 98.8%

* Includes patients admitted to coronary care units and high dependency areas
+ Includes studies performed in an outpatient dialysis population and includes patients on both haemodialysis and peritoneal dialysis
# Includes patients taking ACE-Inhibitors, Angiotensin 2 receptor blockers, Renin inhibitors and Minerallo-corticoid receptor antagonists
^ Includes studies performed across different continents

Table 3: Summary of the pooled mean incidence rate for all combined studies, ages, co-morbidities, study settings, medications and continents and also stratified by study size

	All studies combined	Studies with N <1250	Studies with N ≥1250
Overall			
Incidence – cases per 100-person years (95% CI) I^2 statistic for heterogeneity	2.8 (2.3-3.3) I^2 – 100% Egger's test: p = 0.05	13.5 (7.2-25.3) I^2 – 99.7%	2.3 (1.9-2.7) I^2 – 100%
Age			
All Adults	2.7 (2.3-3.3) I^2 – 100%	13.5 (7.2-25.3) I^2 – 99.7%	2.2 (1.9-2.7) I^2 – 100%
Adults >65	2.4 (1.2-4.9) I^2 – 100%	No studies	2.4 (1.2-4.9) I^2 – 100%
Paediatric	22.0 (15.0-32.4) 1 study	No studies	22.0 (15.0-32.4) 1 study
Neonatal	No studies	No studies	No studies
K+ Severity			
>5.0 mmol/L	8.0 (7.2-8.9) I^2 – 100%	10.3 (4.8-22.4) I^2 – 98.9%	7.9 (7.0-8.8) I^2 – 100%
>5.5 mmol/L	5.9 (3.5-10.0) I^2 – 100%	17.8 (7.9-40.0) I^2 – 99.7%	4.1 (2.2-7.4) I^2 – 100%
>6.0 mmol/L	1.0 (0.8-1.4) I^2 – 99.9%	5.7 (0.6-53.5) I^2 – 99.5%	0.9 (0.7-1.1) I^2 – 100%
ICD Code Only	1.9 (1.1-3.2) I^2 – 100%	No studies	1.9 (1.1-3.2) I^2 – 100%
Co-Morbidity			
CKD-ND	4.2 (3.5-4.9) I^2 – 100%	11.5 (8.2-16.0) I^2 – 96.9%	3.5 (2.9-4.2) I^2 – 100%
>5.0 mmol/L	8.7 (7.7-9.8) I^2 – 99.9%	18.1 (14.0-23.6) I^2 – 20.9%	8.2 (7.2-9.2) I^2 – 99.9%
>5.5 mmol/L	5.9 (4.7-7.4) I^2 – 99.9%	10.1 (6.7-15.3) I^2 – 97.5%	3.8 (2.9-5.0) I^2 – 99.9%
>6.0 mmol/L	2.5 (1.9-3.3) I^2 – 99.7%	2.3 (1.4-3.9) I2 – 82.4%	2.5 (1.9-3.4) I^2 – 99.8%
ESKD	30.0 (14.5-61.9 I^2 – 100%	190.0 (121.9-296.1) I^2 – 97.6%	16.2 (7.0-37.6) I^2 – 100%
>5.0 mmol/L	8.3 (7.9-8.6) 1 study	No studies	8.3 (7.9-8.6) 1 study
>5.5 mmol/L	104.1 (56.3-193.6) I^2 – 100%	242.0 (195.4-299.8) I^2 – 87.7%	68.3 (32.1-145.4) I^2 – 100%
>6.0 mmol/L	9.8 (2.4-40.4) I^2 – 99.9%	90.2 (76.4-106.3) 1 study	3.2 (1.0-10.2) I^2 – 99.8%
Kidney Transplant	4.7 (3.0-7.2) I^2 – 99.3%	13.9 (9.7-20.1) 1 study	4.3 (2.7-6.8) I^2 – 99.4%
>5.0 mmol/L	16.9 (12.0-23.6) I^2 – 98.9%	No studies	16.9 (12.0-23.6) I^2 – 98.9%
>5.5 mmol/L	22.0 (15.0-32.4) 1 study	No studies	22.0 (15.0-32.4) 1 study
>6.0 mmol/L	0.6 (0.5-0.9)	No studies	0.6 (0.5-0.9)

	I^2 – 76.5%		I^2 – 76.5%
Diabetes	1.1 (0.7-1.8) I^2 – 100%	12.5 (5.2-29.9) I^2 – 95.3%	0.9 (0.6-1.5) I^2 – 100%
>5.0 mmol/L	5.0 (2.5-10.1) I^2 – 100%	No studies	5.0 (2.5-10.1) I^2 – 100%
>5.5 mmol/L	3.5 (1.8-7.0) I^2 – 99.9%	12.5 (5.2-29.9) I^2 – 95.3%	1.5 (0.7-3.6) I^2 – 100%
>6.0 mmol/L	0.8 (0.4-1.5) I^2 – 99.7%	No studies	0.8 (0.4-1.5) I^2 – 99.7%
Heart Failure	4.3 (3.1-6.0) I^2 – 100%	2.4 (1.5-3.8) I^2 – 92.3%	5.0 (3.5-7.2) I^2 – 100%
>5.0 mmol/L	13.3 (8.6-20.6) I^2 – 100%	5.8 (4.6-7.3) 1 study	14.9 (9.3-23.8) I^2 – 100%
>5.5 mmol/L	4.2 (2.9-5.9) I^2 – 99.9%	2.9 (2.1-4.2) I^2 – 76.5%	5.0 (3.2-7.8) I^2 – 99.9%
>6.0 mmol/L	1.4 (0.8-2.5) I^2 – 99.8%	0.7 (0.1-4.6) I^2 – 90.7%	1.6 (0.8-3.2) I^2 – 99.9%
Hypertension	3.0 (1.8-5.0) I^2 – 100%	17.6 (6.9-44.9) I^2 – 52.4%	2.5 (1.4-4.2) I^2 – 100%
>5.0 mmol/L	12.1 (3.0-48.7) I^2 – 93.8%	25.8 (12.9-51.6) 1 study	6.2 (6.1-6.3) 1 study
>5.5 mmol/L	2.1 (1.6-2.8) I^2 – 97.9%	9.7 (3.1-30.0) 1 study	2.0 (1.5-2.7) I^2 – 98.2%
>6.0 mmol/L	0.6 (0.5-0.6) 1 study	No studies	0.6 (0.5-0.6) 1 study
AKI	18.3 (17.7-18.8) I^2 – 0%	No studies	18.3 (17.7-18.8) I^2 – 0%
>5.0 mmol/L	No studies	No studies	No studies
>5.5 mmol/L	No studies	No studies	No studies
>6.0 mmol/L	No studies	No studies	No studies
COVID-19	No studies	No studies	No studies
Healthcare Setting			
Outpatient/Primary Care	2.3 (2.1-2.7) I^2 – 100%	8.5 (5.8-12.7) I^2 – 98.7%	2.0 (1.8-2.3) I^2 – 100%
>5.0 mmol/L	8.7 (7.8-9.7) I^2 – 100%	10.3 (4.8-22.4) I^2 – 98.9%	8.6 (7.7-9.7) I^2 – 100%
>5.5 mmol/L	3.4 (2.9-4.0) I^2 – 100%	10.2 (6.1-16.8) I^2 – 98.6%	2.5 (2.1-3.0) I^2 – 100%
>6.0 mmol/L	0.9 (0.7-1.1) I^2 – 99.9%	2.2 (0.2-20.7) I^2 – 98.8%	0.8 (0.7-1.1) I^2 – 99.9%
Emergency Admission	No studies	No studies	No studies
Hospital Inpatient	3.7 (1.4-9.6) I^2 – 99.9%	3.3 (2.2-5.0) 1 study	3.8 (1.3-10.6) I^2 – 99.9%
>5.0 mmol/L	No studies	No studies	No studies
>5.5 mmol/L	5.1 (1.2-22.3) I^2 – 98.7%	3.3 (2.2-5.0) 1 study	6.3 (0.5-72.5) I^2 – 99.3%
>6.0 mmol/L	0.7 (0.6-0.8) 1 study	No studies	0.7 (0.6-0.8) 1 study
Intensive Care*	No studies	No studies	No studies
Dialysis⁺	55.3 (25.1-121.7) I^2 – 100%	190.0 (121.9-296.1) I^2 – 97.6%	29.9 (11.3-78.9) I^2 – 100%
>5.0 mmol/L	No studies	No studies	No studies

>5.5 mmol/L	153.8 (84.5-279.9) I^2 – 100%	242.0 (195.4-299.8) I^2 – 87.7%	117.1 (54.8-250.2) I^2 – 100%
>6.0 mmol/L	22.8 (1.6-106.3) I^2 – 99.9%	90.2 (76.4-106.3) 1 study	5.8 (5.6-6.0) 1 study
Medication Use			
RAASi[#]	1.7 (1.4-2.1) I^2 – 100%	6.8 (1.5-30.5) I^2 – 99.6%	1.5 (1.2-1.9) I^2 – 100%
>5.0 mmol/L	7.6 (6.7-8.7) I^2 – 99.9%	5.8 (4.6-7.3) 1 study	7.7 (6.8-8.9) I^2 – 99.9%
>5.5 mmol/L	3.6 (2.3-5.6) I^2 – 99.9%	13.1 (2.1-79.8) I^2 – 99.6%	2.2 (1.4-3.4) I^2 – 99.9%
>6.0 mmol/L	0.9 (0.5-1.7) I^2 – 99.9%	0.2 (0.1-0.7) 1 study	1.0 (0.5-1.8) I^2 – 99.9%
ACEi	0.7 (0.4-1.1) I^2 – 99.9%	No studies	0.7 (0.4-1.1) I^2 – 99.9%
>5.0 mmol/L	12.3 (8.0-18.9) I^2 – 99.8%	No studies	12.3 (8.0-18.9) I^2 – 99.8%
>5.5 mmol/L	1.3 (0.7-2.3) I^2 – 99.5%	No studies	1.2 (0.7-2.3) I^2 – 99.5%
>6.0 mmol/L	0.4 (0.2-1.1) I^2 – 99.0%	No studies	0.4 (0.2-1.1) I^2 – 99.0%
ARB	1.3 (0.8-2.1) I^2 – 99.9%	4.9 (1.8-13.6) I^2 – 67.2%	1.2 (0.8-1.9) I^2 – 99.9%
>5.0 mmol/L	8.1 (5.2-12.8) I^2 – 99.8%	No studies	8.1 (5.2-12.8) I^2 – 99.8%
>5.5 mmol/L	3.2 (1.3-8.1) I^2 – 99.8%	4.9 (1.8-13.6) I^2 – 67.2%	2.7 (0.9-8.0) I^2 – 99.9%
>6.0 mmol/L	0.8 (0.2-2.8) I^2 – 99.5%	No studies	0.8 (0.2-2.8) I^2 – 99.5%
ACEi/ARB	1.3 (1.1-1.8) I^2 – 100%	6.8 (1.5-30.5) I^2 – 99.6%	1.2 (1.0-1.5) I^2 – 100%
>5.0 mmol/L	7.3 (6.5-8.1) I^2 – 99.8%	5.8 (4.6-7.3) 1 study	7.4 (6.6-8.3) I^2 – 99.8%
>5.5 mmol/L	3.7 (2.3-5.9) I^2 – 99.9%	13.1 (2.1-79.8) I^2 – 99.6%	2.1 (1.3-3.3) I^2 – 99.9%
>6.0 mmol/L	1.0 (0.5-1.8) I^2 – 99.9%	0.2 (0.1-0.7) 1 study	1.0 (0.5-2.0) I^2 – 99.9%
MRA	4.0 (0.2-71.7) I^2 – 99.6%	9.7 (3.1-30.0) 1 study	5.1 (3.3-7.9) I^2 – 99.6%
>5.0 mmol/L	9.9 (2.9-33.6) I^2 – 99.8%	No studies	9.9 (2.9-33.6) I^2 – 99.8%
>5.5 mmol/L	4.0 (0.9-18.0) I^2 – 99.4%	9.7 (3.1-30.0) 1 study	2.8 (0.5-17.0) I^2 – 99.7%
>6.0 mmol/L	0.3 (0.2-0.4 1 study	No studies	0.3 (0.2-0.4) 1 study
Diuretics	4.0 (0.2-71.7) I^2 – 99.9%	17.5 (15.0-20.5) 1 study	0.9 (0.8-1.1) 1 study
>5.0 mmol/L	No studies	No studies	No studies
>5.5 mmol/L	4.0 (0.2-71.7) I^2 – 99.9%	17.5 (15.0-20.5) 1 study	0.9 (0.8-1.1) 1 study
>6.0 mmol/L	No studies	No studies	No studies
CNIs	7.1 (0.8-66.2) I^2 – 99.7%	No studies	7.1 (0.8-66.2) I^2 – 99.7%
>5.0 mmol/L	No studies	No studies	No studies

>5.5 mmol/L	7.1 (0.8-66.2) I^2 – 99.7%	No studies	7.1 (0.8-66.2) I^2 – 99.7%
>6.0 mmol/L	No studies	No studies	No studies
Continent			
Africa	No studies	No studies	No studies
Asia	1.6 (0.8-2.9) I^2 – 99.9%	10.4 (6.0-18.2) I^2 – 80.9%	1.3 (0.7-2.6) I^2 – 100%
>5.0 mmol/L	No studies	No studies	No studies
>5.5 mmol/L	3.8 (0.9-15.9) I^2 – 98.6%	7.9 (5.7-10.9) 1 study	1.7 (1.6-2.0) 1 study
>6.0 mmol/L	0.7 (0.6-0.8) 1 study	No studies	0.7 (0.6-0.8) 1 study
Australasia	5.8 (4.4-7.6) I^2 – 99.5%	No studies	5.8 (4.4-7.6) I^2 – 99.5%
>5.0 mmol/L	7.1 (5.2-9.7) I^2 – 99.3%	No studies	7.1 (5.2-9.7) I^2 – 99.3%
>5.5 mmol/L	No studies	No studies	No studies
>6.0 mmol/L	4.7 (3.1-7.0) I^2 – 99.2%	No studies	4.7 (3.1-7.0) I^2 – 99.2%
Europe	4.1 (3.4-4.9) I^2 – 100%	5.8 (3.6-9.3) I^2 – 98.6%	3.8 (3.1-4.6) I^2 – 100%
>5.0 mmol/L	10.2 (8.8-11.9) I^2 – 100%	10.1 (3.5-29.2) I^2 – 98.5%	10.2 (8.7-12.0) I^2 – 100%
>5.5 mmol/L	4.1 (3.5-4.9) I^2 – 99.9%	7.7 (4.4-13.5) I^2 – 98.5%	3.3 (2.7-4.0) I^2 – 100%
>6.0 mmol/L	1.1 (0.8-1.6) I^2 – 99.9%	0.7 (0.1-4.6) I^2 – 90.7%	1.2 (0.8-1.7) I^2 – 100%
North America	2.3 (1.5-3.6) I^2 – 100%	42.5 (13.2-137.3) I^2 – 99.8%	1.8 (1.0-2.7) I^2 – 100%
>5.0 mmol/L	6.2 (5.3-7.3) I^2 – 99.9%	11.1 (2.3-53.8) I^2 – 95.1%	6.1 (5.2-7.1) I^2 – 99.9%
>5.5 mmol/L	9.1 (3.7-22.2) I^2 – 100%	64.6 (17.7-235.9) I^2 – 99.7%	5.1 (1.8-14.2) I^2 – 100%
>6.0 mmol/L	0.7 (0.4-1.2) I^2 – 99.9%	46.7 (12.6-172.3) I^2 – 97.9%	0.5 (0.3-0.8) I^2 – 99.8%
South America	No studies	No studies	No studies
Global^	9.0 (3.8-21.5) I^2 – 100%	No studies	9.0 (3.8-21.5) I^2 – 100%
>5.0 mmol/L	No studies	No studies	No studies
>5.5 mmol/L	14.0 (13.8-14.3) 1 study	No studies	14.0 (13.8-14.3) 1 study
>6.0 mmol/L	5.8 (5.6-6.0) 1 study	No studies	5.8 (5.6-6.0) 1 study

* Includes patients admitted to coronary care units and high dependency areas
+ Includes studies performed in an outpatient dialysis population and includes patients on both haemodialysis and peritoneal dialysis
# Includes patients taking ACE-Inhibitors, Angiotensin 2 receptor blockers, Renin inhibitors and Minerallo-corticoid receptor antagonists
^ Includes studies performed across different continents

Table 4: Breakdown of studies by study type and continent

	Africa	**Asia**	**Australasia**	**Europe**	**North America**	**South America**	**Global**

Outpatient/ Primary Care	3	50	3	92	93	7	5
Emergency Admissions	4	15	2	17	8	2	0
Hospital Inpatients	5	45	3	44	44	1	2
Intensive Care	0	7	0	10	10	1	0
Dialysis	1	19	0	9	15	4	3
Paediatric	4	10	1	6	6	0	0
Neonatal	1	12	1	2	7	0	0
Total Studies	**14**	**148**	**9**	**176**	**177**	**14**	**10**

Table 5: Breakdown of studies by hyperkalaemia definition including date range of studies using each definition

Definition (mmol/L)	**>4.5**	**>4.7**	**>4.8**	**>5.0**	**>5.2**	**>5.3**	**>=5.5**	**>=5.8**	**>=6.0**	**>6.5**	**>=6.5**	**>=7.0**	**ICD code**	**NR**
Number of studies	7	1	1	203	5	5	241	1	100	2	23	13	39	36
Date range of studies	2006 - 2018	2018	2012	1977 - 2021	2012 - 2020	1997 - 2018	1976 - 2021	2006	1982 - 2021	1992 - 2003	1988 - 2020	1988 - 2019	2003 - 2020	1988 - 2020

Table 6: Hyperkalaemia pooled mean prevalence and pooled mean incidence rate by decade of study publication

Decade of study publication	**1976-1980**	**1981-1990**	**1991-2000**	**2001-2010**	**2011-present**
Prevalence					
Number of studies Percentage of population affected (95% confidence intervals) I^2 statistic for heterogeneity	4 10.3 (3.0-36.1) 98.1%	18 6.4 (4.0-10.4) 99.0%	24 10.9 (7.4-16.2) 98.3%	97 8.7 (7.5-9.9) 99.9%	373 6.2 (5.7-6.8) 100%
Incidence					
Number of studies Cases per 100-person years (95% CI) I^2 statistic for heterogeneity	0 - -	0 - -	3 11.5 (4.3-30.5) 97.3%	5 4.9 (1.2-20.0) 99.9%	55 2.6 (2.2-3.1) 100%

Table 7: Summary of the pooled mean prevalence in different healthcare settings by HK definition, co-morbidity and medications (where number of studies permitted)

	HK by any definition	>5.0 mmol/L	>5.5 mmol/L	>6.0 mmol/L
Outpatient/Primary Care studies				
Overall (number of studies) Percentage of population affected (95% confidence intervals) I^2 statistic for heterogeneity	251 5.0 (4.5-5.5) 100%	110 8.7 (7.8-9.8) 100%	105 5.9 (4.9-7.1) 100%	49 1.7 (1.3-2.3) 99.9%
CKD-Non Dialysis	93 8.1 (7.3-9.0) 100%	45 14.2 (12.1-16.6) 100%	43 (7.2-10.2) 99.9%	18 2.2 (1.6-2.9) 99.8%
Diabetes Mellitus	44 4.5 (3.5-5.8) 99.9%	28 8.3 (5.9-11.6) 100%	18 6.6 (4.0-10.8) 100%	9 (0.6-1.7) 99.1%
Heart Failure	73 6.0 (4.9-7.3) 99.9%	39 8.6 (6.3-11.6) 93.9%	39 7.7 (6.0-9.9) 99.7%	19 2.9 (2.0-4.0) 99.4%
Patients taking RAASi	104 4.6 (4.0-5.4) 99.9%	42 (7.3-10.6) 100%	47 6.6 (5.2-8.4) 99.9%	25 (1.2-3.1) 99.8%
Emergency Admissions				
Overall	49 7.7 (6.1-9.8) 99.8%	17 10.5 (8.1-13.7) 99.7%	20 10.4 (7.4-14.7) 99.8%	8 2.3 (1.5-3.5) 99.3%
CKD-Non Dialysis	4 13.1 (8.6-19.9) 99.6%	3 22.1 (15.8-31.0) 99.0%	2 15.8 (7.9-31.4) 99.4%	1 4.7 (1.9-12.0) 99.1%
Diabetes Mellitus	5 11.0 (6.0-20.3) 99.15	3 7.1 (1.8-28.0) 98.4%	3 19.4 (10.2-37.1) 97.3%	1 4.7 (4.1-5.5) -
Heart Failure	4 6.4 (4.4-9.3) 96.4%	3 6.4 (4.0-10.5) 97.3%	1 8.0 (6.6-9.8) -	2 5.7 (3.1-10.6) 79.1%
Acute Kidney Injury	12 22.4 (13.4-37.4) 98.8%	4 26.2 (13.2-52.1) 95.9%	3 30.0 (6.2-68.6) 99.4%	1 (1.5-3.0) -
Patients taking RAASi	6 7.0 (4.6-9.8) 99.4%	3 14.3 (11.5-17.7) 96.4%	2 4.6 (3.4-6.1) 95.5%	2 (1.5-2.8) 81.3%
Hospital Inpatients				
Overall	144 8.7 (7.8-9.7) 99.9%	40 12.5 (10.1-15.5) 99.9%	65 8.6 (7.4-9.9) 99.8%	17 7.5 (5.4-10.5) 99.5%
CKD-Non Dialysis	9 13.6 (11.3-16.4) 99.6%	4 23.6 (16.4-34.0)	7 11.0 (6.8-18.0) 99.6%	1 13.0 (12.0-14.2)

		99.6%		-
Diabetes Mellitus	8 8.5 (6.1-11.8) 99.7%	3 14.9 (9.4-23.8) 99.1%	6 9.2 (6.3-13.5) 99.2%	1 4.8 (4.4-5.2) -
Heart Failure	20 10.0 (7.6-13.0) 99.4%	5 16.0 (7.9-32.2) 99.7%	14 9.4 (6.7-13.1) 94.9%	3 3.6 (1.3-9.8) 93.4%
Acute Kidney Injury	8 23.6 (16.1-34.6) 99.7%	1 46.4 (45.0-47.8) -	6 28.5 (20.8-39.1) 89.4%	1 10.6 (9.9-11.3) -
Patients taking RAASi	21 12.2 (9.4-15.8) 98.7%	7 20.3 (14.0-29.4) 90.0%	14 11.9 (10.0-14.2) 95.2%	3 9.8 (2.4-39.8) 98.1%

Table 8: Summary of the pooled mean prevalence for all adult studies, co-morbidities, study settings, medications and continents stratified by sex (where study numbers permit)

	Male	Female
Overall		
General Population	1.5 (0.7-3.1) I^2 – 100%	1.2 (0.6-2.5) I^2 – 100%
K^+ Severity		
ICD Code Only	1.9 (0.3-12.3) I^2 – 100%	1.2 (0.2-6.7) I^2 – 100%
Co-Morbidities		
CKD-ND§	10.6 (7.7-14.7) I^2 – 100%	7.9 (5.6-11.2) I^2 – 100%
>5.0 mmol/L	15.8 (10.4-24.1) I^2 – 100%	11.6 (7.6-17.8) I^2 – 100%
>5.5 mmol/L	10.2 (4.2-24.5) I^2 – 100%	7.1 (3.2-16.1) I^2 – 100%
>6.0 mmol/L	0.9 (0.4-2.1) I^2 – 99.1%	0.6 (0.4-1.0) I^2 – 99.6%
ESKD‖	20.7 (16.6-28.3) I^2 – 99.7%	16.9 (14.8-25.5) I^2 – 99.7%
>5.0 mmol/L	20.9 (14.9-29.4) I^2 – 99.6%	17.0 (10.8-26.9) I^2 – 99.8%
>5.5 mmol/L	18.2 (9.7-35.5) I^2 – 99.3%	16.8 (9.2-34.2) I^2 – 99.2%
>6.0 mmol/L	7.7 (7.5-7.9) 1 study	8.3 (8.1-8.5) 1 study
Heart Failure	7.3 (5.6-9.5) I^2 – 99.9%	6.9 (5.2-9.0) I^2 – 99.9%
>5.0 mmol/L	11.9 (8.8-16.2) I^2 – 99.9%	10.6 (7.7-14.5) I^2 – 99.9%
>5.5 mmol/L	4.9 (2.9-8.4) I^2 – 99.7%	4.5 (2.6-7.9) I^2 – 99.7%
>6.0 mmol/L	1.2 (0.3-5.4) I^2 – 98.9%	0.6 (0.1-3.3) I^2 – 99.1%
Hypertension	5.6 (2.2-14.5) I^2 – 100%	3.4 (1.3-8.9) I^2 – 100%
AKI	22.9 (17.9-29.2) I^2 – 72.8%	22.0 (19.0-25.5) I^2 – 41.1%
Healthcare Setting		
Outpatient/Primary Care	4.9 (3.3-7.1) I^2 – 100%	3.8 (2.6-5.7) I^2 – 100%
>5.0 mmol/L	8.5 (6.3-11.3) I^2 – 100%	7.0 (5.2-9.3) I^2 – 100%
>5.5 mmol/L	5.4 (2.7-10.5) I^2 – 100%	4.0 (2.1-7.5) I^2 – 100%
>6.0 mmol/L	0.5 (0.2-1.2) I^2 –99.9%	0.3 (0.2-0.7) I^2 –99.9%
Emergency Admissions	5.7 (3.5-9.5) I^2 – 99.9%	4.9 (2.8-8.3) I^2 – 99.9%
>5.0 mmol/L	5.8 (3.3-10.4) I^2 – 99.8%	5.0 (3.0-8.5) I^2 – 99.8%
>5.5 mmol/L	8.2 (2.3-29.0)	6.9 (1.7-28.2)

	I^2 – 99.9%	I^2 – 99.9%
>6.0 mmol/L	3.0 (0.6-15.5) I^2 – 99.7%	2.5 (0.4-16.8) I^2 – 99.7%
Hospital Inpatients	7.7 (5.9-10.1) I^2 – 99.9%	6.6 (5.0-8.9) I^2 – 99.9%
>5.0 mmol/L	12.6 (7.5-21.2) I^2 – 99.9%	8.0 (3.6-17.9) I^2 – 100%
>5.5 mmol/L	6.0 (4.0-8.8) I^2 – 99.9%	5.5 (3.9-7.8) I^2 – 99.9%
>6.0 mmol/L	5.2 (2.4-11.2) I^2 – 99.4%	5.2 (1.5-17.9) I^2 –99.8%
Intensive Care*	5.8 (4.0-8.6) I^2 – 99.9%	5.3 (3.4-8.3) I^2 – 99.9%
Dialysis[+]	20.2 (15.4-26.6) I^2 – 99.7%	18.5 (14.0-24.3) I^2 – 99.7%
>5.0 mmol/L	20.9 (14.9-29.4) I^2 – 99.6%	17.0 (10.8-26.9) I^2 – 99.8%
>5.5 mmol/L	18.2 (9.7-35.5) I^2 – 99.3%	16.8 (9.2-34.2) I^2 – 99.2%
>6.0 mmol/L	7.7 (7.5-7.9) 1 study	8.3 (8.1-8.5) 1 study
Medication Use		
RAASi[#]	9.4 (5.4-16.3) I^2 – 100%	8.2 (4.5-15.0) I^2 – 100%
>5.0 mmol/L	21.6 (13.3-35.1) I^2 – 100%	17.7 (10.9-28.5) I^2 – 100%
>5.5 mmol/L	7.8 (4.7-13.0) I^2 – 99.2%	6.6 (4.1-10.7) I^2 – 98.9%
ACEi	7.7 (4.4-13.4) I^2 – 98.0%	5.9 (3.3-10.5) I^2 – 98.2%
ARB	8.1 (1.5-33.8) I^2 – 100%	8.3 (1.3-45.2) I^2 – 100%
MRA	13.2 (7.0-24.8) I^2 – 97.3%	12.6 (3.6-43.7) I^2 – 98.4%
Diuretics	5.7 (3.1-10.4) I^2 – 99.6%	5.8 (2.9-11.6) I^2 – 99.7%
CNIs	7.1 (6.7-7.5) 1 study	6.7 (6.3-7.1) 1 study
Continent		
Africa	28.9 (18.4-45.3) I^2 – 44.1%	19.8 (8.8-44.3) I^2 – 74.1%
Asia	15.1 (10.5-21.8) I^2 – 99.3%	14.6 (10.1-21.1) I^2 – 99.3%
Australasia	8.7 (2.9-25.7) I^2 – 99.9%	5.7 (1.8-17.9) I^2 – 99.9%
Europe	5.7 (4.3-7.7) I^2 – 100%	5.1 (3.9-6.6) I^2 – 100%
>5.0 mmol/L	7.6 (5.5-10.5) I^2 – 100%	6.7 (5.0-9.0) I^2 – 100%
>5.5 mmol/L	6.5 (3.3-12.8) I^2 – 100%	5.7 (3.0-10.9) I^2 – 100%
>6.0 mmol/L	0.9 (0.3-2.9) I^2 – 99.9%	0.8 (0.3-2.4) I^2 – 99.9%
North America	4.5 (2.8-7.3)	3.1 (1.9-5.1)

	I^2 – 100%	I^2 – 100%
>5.0 mmol/L	8.7 (6.0-12.7) I^2 – 100%	6.7 (4.4-10.3) I^2 – 100%
>5.5 mmol/L	4.2 (2.4-7.2) I^2 – 100%	2.8 (1.7-4.8) I^2 – 100%
>6.0 mmol/L	1.6 (0.5-5.9) I^2 – 100%	1.1 (0.2-4.5) I^2 – 100%
South America	23.1 (4.7-52.1) I^2 – 99.2%	18.8 (3.6-49.2) I^2 – 99.3%
Global^	14.7 (4.1-28.1) I^2 – 100%	15.4 (4.6-28.7) I^2 – 100%

§ Includes patients with pre-dialysis CKD 5 (eGFR<15)
|| Includes patients from ANY study setting receiving kidney-replacement therapy but NOT pre-dialysis CKD5 or those with a kidney transplant
* Includes patients admitted to coronary care units and high dependency areas
+ Includes studies performed in an outpatient dialysis population and includes patients on both haemodialysis and peritoneal dialysis
# Includes patients taking ACE-Inhibitors, Angiotensin 2 receptor blockers, Renin inhibitors and Minerallo-corticoid receptor antagonists
^ Includes studies performed across different continents

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APPENDIX 3

SUPPLEMENTARY MEDIA PUBLICATIONS

SUPPLEMENTARY MEDIA PUBLICATIONS

https://www.sun.ac.za/english/Lists/news/DispForm.aspx?ID=9116

SU study sheds light on treatment of hyperkalaemia

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Medical specialists urgently need more knowledge on how to treat and manage hyperkalaemia (too much potassium in the blood), which may cause respiratory muscle weakness and potentially fatal heart rhythm disturbance.

This is according to a new study at Stellenbosch University (SU).

“We found that there is a paucity of data on the knowledge and practice patterns of medical specialists regarding the emergency management of hyperkalaemia. There is also a lack of consensus regarding the best way to manage it, which may result in wide variations in practice and the guidance provided to junior staff," says Dr Yazied Chothia, senior lecturer and nephrologist in the Division of Nephrology in the Department of Medicine at SU's Faculty of Medicine and Health Sciences. He conducted the research with colleagues Prof Usuf Chikte (Division of Health Systems and Public Health, Department of Global Health) and Dr Razeen Davids (Division of Nephrology, Department of Medicine).

They conducted the first comprehensive survey in South Africa among specialists in nephrology, internal medicine, emergency medicine and critical-care medicine to evaluate their knowledge regarding the diagnosis and management of hyperkalaemia, with a focus on insulin-based therapy. Insulin-based therapy is the most favoured pharmacological method for treating hyperkalaemia. Dextrose (a type of sugar) is usually co-administered to prevent low blood sugar (hypoglycaemia).

“Our aim was to identify knowledge gaps and to inform the development of learning resources to guide the optimal management of this life-threatening condition."

The findings of their study were published recently in the **African Journal of Nephrology**.

According to the researchers, various recommendations exist regarding the dosing, sequence and rates of administration for insulin and dextrose to treat hyperkalaemia.

They identified important shortcomings regarding the knowledge and management of hyperkalaemia among medical specialists.

“These included tented T waves as the most common electrocardiogram (ECG) change (change in heart rhythm) to trigger therapy, the time for the potassium concentration to reach its nadir following insulin administration, whether the potassium concentration would return to its pre-shift value and when this was expected to occur, defining resistant hyperkalaemia, and the expectation and surveillance of hypoglycaemia following insulin-based therapy.

“Two-thirds of respondents routinely performed an ECG before deciding whether a patient required treatment for hyperkalaemia, with more non-nephrologists performing an ECG.

Nearly three quarters of respondents thought that there was a poor correlation between potassium and the presence of ECG changes."

The researchers add that nephrologists tended to start therapy at a higher range of serum potassium/potassium in the blood (6,0–6,5 millimoles per litre [mmol/L]), defined by many as moderate to severe hyperkalaemia.

"We speculate that this is because of the high frequency with which they encounter patients with severe hyperkalaemia.

"Regarding pharmacological therapy, all the respondents indicated that they regarded insulin and dextrose therapy as the most effective and reliable method for shifting potassium into cells. This was not surprising because insulin-based therapy is regarded by most authorities as the cornerstone of treatment."

According to researchers, fewer than half of the respondents were aware that serum potassium would reach its nadir at 60 minutes after insulin was administered and less than two-thirds indicated that they anticipated the potassium value to return to its pre-shift value. Only a third expected this to occur at 4–6 hours following insulin therapy.

"Of concern was the low expectation of hypoglycaemia by respondents, with only 14% anticipating hypoglycaemia between 2–3 hours after insulin had been administered and 22% indicating that hypoglycaemia was uncommon if dextrose was co-administered. Only 30% checked the glucose concentration in the blood at two hours, and only 22% at three hours."

Recommendations

Based on the knowledge gaps that they have identified, the researchers make a few recommendations that could help medical specialists in the treatment and management of hyperkalaemia.

They say medical specialists should start therapy when potassium is higher or equal to 6 mmol/L or when they noticed any degree of hyperkalaemia which is accompanied by symptoms or ECG changes.

"An ECG should be performed on all patients. Calcium salts should be administered only when there are ECG changes. Calcium salts are used to protect the heart from the dangerous effects of hyperkalaemia.

"Short-acting insulin should be administered as a push (bolus) of 10 units, intravenously. Lower doses (five units) should be considered in patients with chronic kidney disease and kidney failure.

"Patients should be monitored for symptoms of hypoglycaemia and serum glucose concentrations should be measured hourly for at least three hours, and up to six hours, following insulin-based therapy. The potassium concentration should be checked one hour following insulin-based therapy as this is when the nadir is expected."

The researchers say their study emphasises the need to address knowledge gaps, particularly around the optimal and safe use of insulin-based therapies. "Our findings and recommendations should be useful in informing the development of consensus guidelines and educational resources on hyperkalaemia."

- **Source**: Chothia M-Y, Chikte U, & Davids MR 2022. Knowledge of medical specialists on the emergency management of hyperkalaemia with a focus on insulin-based therapy. *African Journal of Nephrology*. Volume 25, No 1, 2022, 14-25: DOI: **https://doi.org/10.21804/25-1-5002**