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REVIEW

Correlation of acidosis-adjusted potassium level and cardiovascular outcomes in diabetic ketoacidosis: a systematic review

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Background: During the progress and resolution of a diabetic ketoacidosis (DKA) episode, potassium levels are significantly affected by the extent of acidosis. However, none of the current guidelines take into account acidosis during resuscitation of potassium level in DKA management, which may increase the risk of cardiovascular adverse events.

Objective: To assess literature regarding the adjustment of potassium level using pH to calculate pH-adjusted corrected potassium level, and to observe the relationship of cardiovascular outcomes with reported potassium level and pH-adjusted corrected potassium in DKA.

Methodology: Seven databases were searched from inception to January 2018 for studies which had reported people with diabetes developing diabetic ketoacidosis, in relation to prevalence or incidence, fluid resuscitation or potassium supplementation treatment, treatment or cardiovascular outcomes, and experimentation with DKA management or insulin. Quality of studies was evaluated using Cochrane Risk of Bias and Newcastle Ottawa Scale.

Results: Forty-seven studies were included in qualitative synthesis out of a total of 10,292 retrieved studies. Forty-one studies discussed the potassium level and blood pH at the time of admission, ten studies discussed cardiovascular outcomes, and only four studies concurrently discussed potassium level, pH, and cardiovascular outcomes. Only two studies were graded as good on the Newcastle Ottawa Scale. The reported potassium level was well within normal range (5.8 mmol/L), whereas pH rendered patients to be moderately acidotic (7.13). Surprisingly, none of the included studies mentioned pH-adjusted corrected potassium level and, hence, this was calculated later. Although mean corrected potassium was within the normal range (3.56 mmol/L), 13 studies had corrected potassium below 3.5 mmol/L and five had it below 3.0 mmol/L. Nevertheless, with the exception of one study, none discussed cardiovascular outcomes in the context of potassium or pH-adjusted potassium level.

Conclusion: The evidence surrounding cardiovascular outcomes during DKA episodes in light of a pH-adjusted corrected potassium level is scarce. A prospective observational, or preferably, an experimental study in this regard will ensure we can modify and enhance safety of existing DKA treatment protocols.

Keywords: diabetic ketoacidosis, potassium, hypokalemia, blood gasses, acidosis, pH, treatment outcomes, cardiovascular, insulin

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Background

Diabetic ketoacidosis

Diabetic ketoacidosis is a prevalent acute hyperglycemic complication of diabetes mellitus.[1,2] It is a severe and life threatening complication, and requires immediate therapeutic interventions which may otherwise lead to a fatal outcome.[3] The most

common causes of any DKA episode are poor compliance, infection, and physical stress, ie, cardiovascular (CV) disorder.[2,3] Initial insulin deficiency causes hyperglycemia, ketonemia, and acidosis, all of which promote diuresis. This causes notable hypovolemia and loss of electrolytes. In response to the metabolic and hypovolemic stress, the concentration of counter regulatory hormones (CRH), ie, catecholamines, increases significantly. Increase in CRH further exacerbates circulatory distress.[4] Metabolic, hormonal, and circulatory impairment in DKA requires swift action. In this regard, recommended treatment of DKA encompass of correction of blood volume, achieving euglycemia, and restoration of normal pH utilizing intravenous fluid resuscitation, insulin, and bicarbonate buffer, respectively.[4–7]

Potassium in diabetic ketoacidosis

Hypokalemia is a frequently observed complication in DKA. The role of potassium during an episode of DKA is very crucial where the abovementioned factors have an arguable influence on its regulation.[8–10] Initially, DKA patients experience hyperkalemia; insulin deficiency renders cellular inability to allow potassium re-entry into the cell, and catecholamines induced cellular insensitivity hinders cellular uptake of potassium.[11] Upon further progress, acidosis causes desensitization of cognate receptors of insulin and catecholamines, resulting in exacerbating hyperkalemia.[12] Nevertheless, hyperkalemia swiftly changes to hypokalemia. Primary renal clearance of excessive glucose, and secondary renal clearance of ketone bodies cause polyurea and hypovolemia. In order to maintain homeostasis, the kidneys retain sodium and bicarbonate at the expense of potassium excretion.[10,13] Diuresis induced by hyperglycemia and ketosis alone depletes as much as 3–15 mmol/kg of potassium.[14,15] Additionally, hyperkalemia-induced vomiting in DKA causes a loss of potassium too.[16]

Potassium in cardiovascular outcomes

Cardiovascular disorders are also among precipitating factors of DKA whereby they cause physical stress in DM patients.[17] Among CV disorders, myocardial infarction (MI) is the most observed cardiac incident which triggers an episode of DKA.[1–3,18] Moreover, the concentration of CRH increases significantly during acidosis, which further increases the risk of adverse CV outcome in DKA patients. Although an episode of MI may not be directly associated with potassium level, potassium remains an important repolarization electrolyte in the cardiac cycle. At any point of an episode of acute MI, the level of potassium is often considered crucial as the patient may also experience life threatening arrhythmia secondary to catecholamine driven influx of potassium ion.[19,20] Physiologic effects of hypokalemia involving pulse induction are altered primarily due to changes in refractory periods of myocardia, and result in the form of premature ventricular contractions, fibrillation, and tachycardia. These effects are also visible when considering an electrocardiograph (ECG) in DKA patients; a relative flat ST with a prominent U wave fusing with a T wave is observed among patients with DKA experiencing hypokalemia.[21,22] This leads to the notion that ECG and CVS stability shall also be considered as prime objectives when treating a DKA patient.

Rationale and objectives

The consequences of hypokalemia accompanied by acidosis are relatively deleterious when physiologic cardiac conduction is hindered.[19,23] Moreover, deterioration of a patient's condition may be observed when pH impairs the regular function of insulin and catecholamines. On the other hand, besides that acidosis is a major factor for hypokalemia in DKA, it also has CVS suppressive effects.[11] Hydrogen ions reduce cardiac output and peripheral vasodilation, hinder inotropic effect, and cause bradycardia. Additionally, the association of outcomes of DKA patients with elevated cardiac troponin I, although not extensive, somehow depicts that CVS does undergo enormous stress during a DKA episode.[24] All these effects of DKA on CVS encourage us to signify the effect of potassium on CV outcomes in light of acidosis in DKA patients. Hence, this systematic review aims to explore the difference between reported potassium level and pH-adjusted corrected potassium level among the DKA patients. Second, it also focuses on reports of CV complications among DKA patients and its correlation with admission and pH-adjusted corrected potassium level.

Methodology

A systematic review of the published literature was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] Seven databases – EBSCOhost, PubMed, Scopus, Ovid databases (Cochrane, Embase, and MEDLINE), and clinical trial registries – were searched from the date of inception until January 30, 2018. Main MeSH terms for DKA, adapted form Andrade-Castellanos

CA et al,[26] were as follows: "Diabetic ketoacidosis", "Diabetic Coma", and (Hyperglycaemic OR Hyperglycemic OR Diabet* AND (Keto* OR acidos* OR coma) OR Emergen*) OR DKA. Similarly, MeSH terms related to treatment, treatment modalities, the outcome of treatment, and potassium were adapted from Tran et al.[27] Finally, terms for insulin and cardiovascular were added to conclude the search. All the terms were connected with relevant key words of varying management aspects of DKA (Supplement). Boolean operators were used to combine text terms, keywords, and MeSH terms. This was further supplemented by a backward and forward manual search of relevant references. Once finalized, search terms were evaluated by TMK, NM, IR, and AB.

Registration of study protocol

The protocol was registered with PROSPERO (Registration Number: CRD42018098772).

Study selection

An article was included if it met the following criteria: 1) the study reported the prevalence of DKA in adult diabetic patients and assessed admission potassium level and pH; 2) the study qualitatively observed cardiovascular outcomes in DKA patients; 3) the design of the study was a cross-sectional or cohort, or randomized controlled trial. Studies were excluded if 1) it was a case-control, case report, conference proceeding, systematic review, letter to editor, an opinion, or research brief; 2) published in languages other than English; 3) reported DKA secondary to pregnancy or among pediatrics, or 4) studies evaluating therapeutic intervention which includes DKA secondary to sodium-glucose co-transporter 2 inhibitor.

Outcomes of interest

Primary outcome

Level of serum potassium, and pH-adjusted corrected level of potassium at the time of admission.

Secondary outcome

Cardiovascular outcomes in relation to potassium in DKA episode

Specifically, the CV outcomes were noted in relation to the level of potassium at the time of occurrence of CV event and included ECG, report of fibrillation, tachycardia or bradycardia, central venous pressure, cardiac arrest, myocardial infarction, and troponin. Moreover, reports of CV outcomes or signs and symptoms were recorded if the CV outcome was reported as the reason for fatality. It was further noted if any relationship was given by the authors between hypokalemia and the reason for such CV outcome.

Data extraction and synthesis

All references retrieved were initially grouped under the respective search engine. Duplicates were removed, and titles were screened for eligibility. After removal of irrelevant studies, regrouping was done according to the nature of the study, ie, case series, clinical trial, guideline, etc. Relevant demographic, scientific, and clinical information was recorded in a separate data extraction sheet (Supplement). Later, the level of corrected potassium was calculated by subtracting 0.6 mmol/L from the reported potassium level against each 0.1 decreases in arterial pH from 7.4.[15]

Two of the authors (AU and TMK) independently reviewed the titles and abstracts of all identified studies to determine the articles that were suitable for further consideration. Disagreements were resolved by discussion among AU and TMK. A standardized form was used to extract the data from selected studies which included authors, year of publication, country of conduct of the study, region of the country, study objectives, sample size, the duration for study, study design and nature, and level of reported potassium and pH (Supplement). The extracted data was subsequently reviewed independently by IR and AB, whereas verification of extraction was done by TMK, NM, and MMB. Disagreements encountered in data synthesis, if any, were resolved by discussion between AU and TMK, and IR and AB. The value of the pH-adjusted corrected potassium level was later added to the respective study.

Quality assessment

The quality of randomized clinical trials was assessed using the Cochrane risk of bias tool,[28] while observational studies were assessed by using the Newcastle Ottawa Scale for cross-sectional and cohort studies.[29,30] For Cochrane risk of bias, bias that was likely to affect the results seriously was graded as high risk, bias that was unlikely to affect results seriously was graded as low risk, and bias that was likely to raise doubts regarding results was graded as unclear bias.[28]

The Newcastle Ottawa scale for cross-sectional studies was scored as: "selection (up to 4 points), comparability (up to 2 points), and outcome (up to 3 points)".[29] A similar standard was used for the Newcastle Ottawa scale for cohort studies as

well.[30] Overall, the study quality was labeled as poor (score ≤3), fair (score 4–6), and good (score ≥7). Quality assessment was solely done by AU and independently reviewed by IR, AB, and TMK. Lastly, TMK and SLWH resolved disagreements from quality assessment through discussion.

Results

Study selection

The search identified 5,083 studies after removing duplicates (5,229) and title screening (2,968) (Figure 1). Of these, 2,115 studies were selected for abstract screening. A total of 2,039 studies were excluded as they did not have relevant data related to DKA (502), were reviews (440), were published in a language other than English (205), or either had a patient pool of pregnant or pediatric patients (228). The review is concluded on 47 studies.[9,16,21,31–74]

Characteristics of included full-text retrievals

Of the total 47 research articles, 24[9,21,33,39,45,47–49,51–53,56,58–60,62–64,68–71,73,74] were cross-sectional case series mainly describing retrospective data on either prevalence or simple characteristics of DKA patients upon admission (Table 1). Two of the studies[38,65] were cohorts of DKA patients further divided on the basis of treatment intervention given at a given time and retrospectively evaluated for the efficacy or safety of the said treatment intervention. Seven studies[37,40,41,43,55,57,67] were clinical trials that prospectively measured such effects; however, only five of these studies[40,43,55,57,67] were randomized control trials. Only 37 of the studies concurrently reported the value of pH and potassium,[16,34,35,37,40–44,46–50,52–74] six provided only CV outcomes,[9,31–33,36,45] and only four[21,38,39,51] discussed potassium, pH, and CV outcomes concurrently (Table 1).

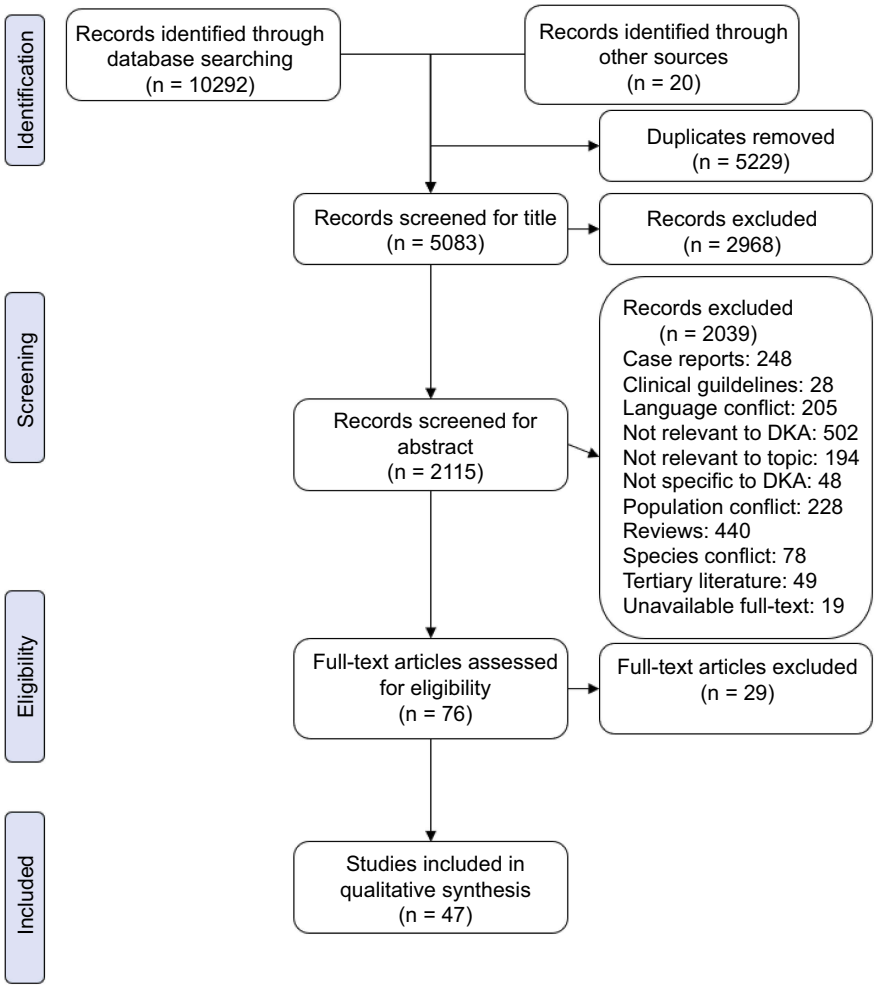

Figure 1 PRISMA flow chart of inclusion and exclusion of studies in systematic review.
Note: Adapted from PRISMA.[25]
Abbreviation: DKA, diabetic ketoacidosis.

Table 1 Basic characteristics of included studies

Authors	Year of publication	Origin of study	Objectives of study	Patient number	Study design	Nature of data	Objectives met	NOS
Baker[31]	1936	France	Review profiles of DKA patients and pattern of treatment after discovery of insulin.	108	Case Series	Retrospective	2	1
Cohen et al[32]	1960	USA	Effect of appropriate use of insulin, antibiotic, electrolytes in reduction of mortality.	73	Cross-sectional	Prospective	2	2
Beigelman[33]	1971	USA	Analyse admission profiles of DKA patients and study the factors associated with mortality.	482	Cross-sectional	Retrospective	2	3*
Assal et al[34]	1973	USA	Evaluate effects of HCO_3^- given in conjunction of insulin and normal saline.	9	Cohort	Prospective	1	2^+
Genuth[35]	1973	USA	Study effects of constant insulin given extracellularly in case of severe insulin deficiency.	11	Cross-sectional	Prospective	1	2
Page et al[36]	1974	UK	Elaborate results of using continuous low-dose IV insulin infusion during treatment of DKA.	31	Cross-sectional	Prospective	2	2
Semple et al[37]	1974	UK	Study the effects of maintaining plasma levels of insulin by using IV insulin.	13	Unblinded Cohort	Prospective	1	2^+
Keller et al[38]	1975	Switzerland	Evaluate risk factors leading to severe DKA related mortality using camparable therapy.	58	Cohort	Retrospective	1 and 2	2^+
Asplin[39]	1975	UK	Study effects of low-dose insulin in DKA.	22	Cross-sectional	Retrospective	1 and 2	3
Kitabchi et al[40]	1976	USA	Compare low-dose IM insulin with high-dose IV or s/c insulin in DKA.	48	Randomized Control	Prospective	1	†
Lutterman et al[41]	1979	USA	Compare high-dose insulin therapy and HCO_3^- with low-dose insulin without HCO_3^- at pH below 7.0.	24	Unblinded Cohort	Prospective	1	2^{*+}
Pfeifer et al[42]	1979	USA	Report profiles of DKA patients comparing low-dose vs high-dose insulin in treatment of DKA.	6	Case Series	Prospective	1	2
Sacks et al[43]	1979	USA	Compare priming dose-intermittent IM insulin with a dose-sustaining IV albumin-free insulin.	30	Randomized Control	Prospective	1	†
Owne et al[44]	1981	USA	Quantitatively record renal excretion of glucose, ketones, and nitrogenous compounds in DKA.	10	Cohort	Retrospective	1	1^{*+}

(*Continued*)

Table 1 (Continued).

Authors	Year of publication	Origin of study	Objectives of study	Patient number	Study design	Nature of data	Objectives met	NOS
Adrogue et al[16]	1986	USA	Examine role of blood gasses, renal profile, and blood urea nitrogen on potassium in DKA.	54	Cross-sectional	n/a	1	4
Basu et al[45]	1992	UK	Study outcomes, trends, and reasons of mortality in DKA.	929	Cross-sectional	Retrospective	2	4
Rajasoorya et al[46]	1993	Singapore	Assess the characteristics of DKA in population base setup.	33	Cross-sectional	n/a	1	2
Chu et al[47]	1997	Taiwan	Record admission profiles of DKA patients in T2DM.	137	Cross-sectional	Retrospective	1	4*
Singh et al[48]	1997	UK	Document causes, incidence, complications, and quality of management of DKA.	71	Cross-sectional	Retrospective	1	4
Wagner et al[49]	1999	Germany	Outline concept of DKA therapy to reduce DKA complications and mortality.	114	Cross-sectional	Retrospective	1	1
Umpierrez and Freire[50]	2002	USA	Determine prevelance of abdominal pain and its clinical significance in hyperglycemic patients.	189	Cross-sectional	Prospective	1	4
Jabbar et al[51]	2004	Pakistan	Record admission profiles of and treatment outcome for DKA patients in T2DM.	114	Cross-sectional	Retrospective	1 and 2	4
Newton and Raskin[52]	2004	USA	Compare clinical and biochemical profiles of DKA patients of T2DM with T1DM.	176	Cross-sectional	Retrospective	1	3
Lin et al[53]	2005	Taiwan	Review presenting profiles and outcomes of treatment of DKA patients.	148	Cross-sectional	Retrospective	1	3
Solá et al[54]	2006	Spain	Record causes, incidence and complications of DKA and its treatment quality.	153	Cross-sectional	Prospective	1	3
Ersöz et al[55]	2006	Turkey	Compare efficacy and safety of s/c insulin lispro against standard IV insulin in DKA.	20	Randomized Control	Prospective	1	†
Abela et al[56]	2008	Malta	Assess protocol used to treat DKA to develop new guideline.	56	Cross-sectional	Retrospective	1	3
Kitabchi et al[57]	2008	USA	Compare efficacy of insulin priming dose with CII with two different CII without priming dose.	37	Randomized Cohort	Prospective	1	†
Huri et al[58]	2009	Malaysia	Establish admission profiles of DKA patients in T1DM and T2DM.	265	Cross-sectional	Retrospective	1	3*

(*Continued*)

Table 1 (Continued).

Authors	Year of publication	Origin of study	Objectives of study	Patient number	Study design	Nature of data	Objectives met	NOS
Lopes et al[59]	2011	Brazil	Document evolution of DKA patients' metabolic acidosis admitted to ICU.	9	Cross-sectional	Retrospective	1	2
Robles et al[60]	2011	Brazil	Study accuracy of K^+ retrieved from blood gas analysis and compare it with laboratory serum K^+.	53	Cross-sectional	Retrospective	1	5
Al-Rubeaan et al[61]	2011	Saudi Arabia	Record admission characteristics of DKA patients.	240	Observational	Prospective	1	3*
Chua et al[62]	2012	Australia	Assess safety and efficacy of plasma lyte in comparison with normal saline in DKA treatment.	23	Cross-sectional	Retrospective	1	5*
Weinert et al[63]	2012	Brazil	Record precipitating factors of DKA in middle-income country.	80	Cross-sectional	Retrospective	1	5
Duhon et al[64]	2013	USA	Establish outcomes for DKA patients with concurrent use of HCO_3^- therapy.	86	Cross-sectional	Retrospective	1	7* †
Azevedo et al[65]	2014	Canada	Charaterize admission profiles of moderate-to-severe DKA patients.	76	Matched Cohort	Retrospective	1	7* +
Seth et al[66]	2015	India	Study admission characteristics of DKA patients.	60	Cross-sectional	Prospective	1	4
Houshyar et al[67]	2015	Iran	Establish efficacy of glargine insulin during DKA treatment.	16	Randomized Control	Prospective	1	†
Usman et al[68]	2015	Malaysia	Record incidence and clinical chemistry of DKA patients and its treatment outcomes.	132	Cross-sectional	Retrospective	1	5
Guisado-Vasco et al[69]	2015	Spain	Record mortality rate, length of stay, and factors leading to ICU admission among DKA patients.	164	Cross-sectional	Retrospective	1	6* ‡
Navarro-Diaz et al[70]	2015	Spain	Record emidemiological data of DKA and physicians' adherence to treatment guideline of DKA.	49	Cross-sectional	Retrospective	1	5
Wong et al[9]	2016	Canada	Establish prevalence and factors associated with hypokalemia in DKA patients.	40	Cross-sectional	Retrospective	2	5
Dhatariya et al[71]	2016	UK	Survey and assess DKA management nationally in light of JBDS.	283	Cross-sectional	Retrospective	1	2
Talebi et al[21]	2016	USA	Confirmation of ECG as initial marker of hypokalemia in DKA patients.	61	Cross-sectional	Retrospective	1 and 2	6

(*Continued*)

Table 1 (Continued).

Authors	Year of publication	Origin of study	Objectives of study	Patient number	Study design	Nature of data	Objectives met	NOS
Kakusa et al[72]	2016	Zambia	Record clinical characteristics of DM patients when admitted for DKA, and predictors of outcomes.	80	Cross-sectional	Prospective	I	5*
Kamata et al[73]	2017	Japan	Identify precipitating factors, clinical characteristics, and successful modalities of therapy in T2DM DKA patients.	211	Cross-sectional	Retrospective	I	6
Balili and Gomez[74]	2017	Philippines	Compare intermittent s/c insulin with CII in mild-to-moderate DKA in terms of safety and efficacy.	30	Cross-sectional	Retrospective	I	6*

Notes: Study scored for: *controlling confounding factors between/among groups; †comparability between respondent and non-respondent group; ‡sample size calculated. Newcastle-Ottawa Scale (NOS) for Cross-Sectional Studies was used for quality assessment, with the exception of '+' where NOS for cohort studies was used for Cohort Studies; †refer to Figure 2 for Cochrane Risk of Bias.

Abbreviations: DKA: Diabetic ketoacidosis; HCO3-: Bicarbonate; IV: Intravenous; IM: Intramuscular; s/c: Subcutaneous; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; CII: Continuous insulin infusion; ICU: Intensive care unit; K+: Potassium; JBDS: Joint British Diabetic Society; ECG: Electrocardiogram; DM: Diabetes Mellitus.

Quality of the included studies

In terms of quality of the studies, 22 studies[31–39,41,42,44,46,49,52–54,56,58,59,61,71] scored poor, 18 studies[9,16,21,45,47,48,50,51,60,62,63,66,68–70,72–74] scored fair, and two studies[64,65] scored good on NOS. Among studies scoring 5, four [43,55,62,72] were scored on the basis of comparability by controlling confounding factors between the groups as well. Similarly, of the studies that scored 3 and 4 on NOS, three studies[33,58,61] from score 3, and two studies[47,57] from score 4 were also scored for controlling confounding factors between the groups (Table 1 footnote). Of four studies that established comparability between respondents and non-respondents, one each scored 4[40] and 6[57] on NOS and two scored 7.[64,67] Notably, there was only one study that defined the sample size in terms of calculating on the basis of prevalence of DKA.[69]

The Cochrane Risk of Bias tool was used to assess five studies.[40,43,55,57,67] None of the studies was completely blinded for participants (Figure 2). In the context of blinding of outcomes, only two of the studies[55,67] predefined outcomes for assessment of endpoints. Among these studies, the least reporting bias was observed in the study by Ersöz et al,[55] while the rest of the studies were found with a moderate risk of bias.[40,43,57,67]

Data analysis: potassium, pH, and pH-adjusted corrected potassium

Concurrently, the level of potassium and pH was only available in 41 studies[16,21,34,35,37–44,46–74] (Table 2). The least actual

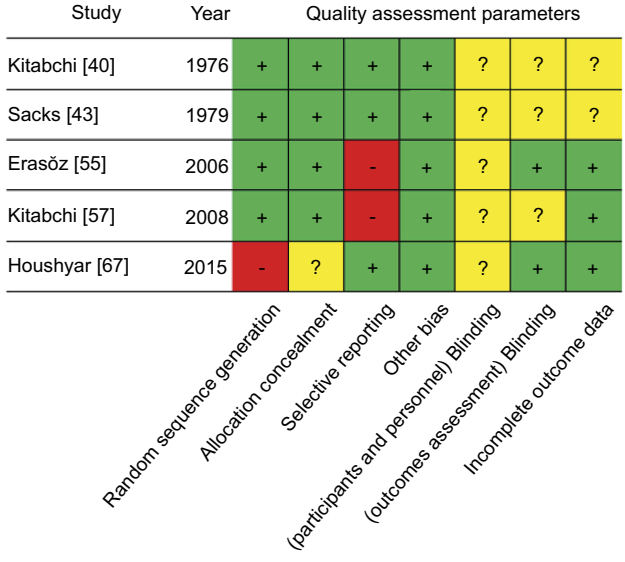

Figure 2 Cochrane Risk of Bias for included clinical trials.

Table 2 Measure and pH adjusted potassium level in the included studies grouped on the basis of region

Authors	Region	Patient number	Reported K^+ level mean (SD/IQR)	Region-wise K^+ level mmol/L	Admission pH mean (SD/IQR)	Region-wise pH level	Calculated potassium	Regional calculated K^+ mmol/L
Rajasoorya et al[46]	Far Eastern	979	5.1 (1.1)	4.9 (0.44)	7.15 (0.16)	7.15 (0.065)	3.9	3.65 (0.38)
Chu et al[47]	Far Eastern		4.78 (1.0)		7.14 (0.25)		3.52	
Lin et al[53]	Far Eastern		4.6 (1.0)		7.13 (0.11)		3.28	
Huri et al[58]	Far Eastern		5.22 (1.43)		7.22 (0.14)		4.22	
Chua et al[62]	Far Eastern		5.5 (3.5–7.3)		7.02 (6.9–7.13)		3.52	
Usman et al[68]	Far Eastern		4.3 (1.2)		7.15 (0.16)		3.1	
Kamata et al[73]	Far Eastern		5.2 (1.2)		7.16 (0.14)		4.06	
Balili et al[74]	Far Eastern		4.3 (1.0)		7.24 (0.13)		3.64	
Jabbar et al[51]	Mid-Eastern	586	4.9 (1.2)	4.4 (0.51)	7.07 (0.11)	7.17 (0.023)	3.22	3.34 (0.50)
Ersöz et al[55]	Mid-Eastern		4.8 (0.7)		7.16 (0.12)		3.76	
Abela et al[56]	Mid-Eastern		3.4 (n/a)		7.19 (7.1–7.2)		2.4	
Al-Rubeaan et al[61]	Mid-Eastern		4.5 (0.8)		7.20 (0.10)		3.6	
Seth et al[66]	Mid-Eastern		4.5 (n/a)		7.23 (n/a)		3.83	
Houshyar et al[67]	Mid-Eastern		4.6 (0.6)		7.09 (0.15)		3.04	
Kakusa et al[72]	Mid-Eastern		4.1 (1.8)		7.26 (0.15)		3.56	
Semple et al[37]	Mid-Western	1995	5.3 (1.1)	4.9 (0.31)	7.07 (0.18)	7.12 (0.058)	3.62	3.51 (0.28)
Keller et al[38]	Mid-Western		5.0 (1.3)		7.00 (0.20)		2.9	
Asplin[39]	Mid-Western		4.2 (1.0)		7.19 (0.13)		3.24	
Singh et al[48]	Mid-Western		5.0 (3.5–8.0)		7.16 (6.57–7.32)		3.86	
Wagner et al[49]	Mid-Western		5.1 (0.9)		7.13 (0.13)		3.78	
Solá et al[54]	Mid-Western		4.9 (0.96)		7.12 (0.12)		3.52	
Dhatariya et al[71]	Mid-Western		4.8 (1.0)		7.16 (0.15)		3.6	
Guisado-Vasco et al[69]	Mid-Western		4.76 (0.98)		7.16 (0.19)		3.62	
Navarro-Diaz et al[70]	Mid-Western		5.0 (3.3–8.0)		7.10 (6.4–7.3)		3.5	
Assal et al[34]	Far Western	1554	5.6 (0.3)	5.1 (0.45)	7.06 (0.03)	7.11 (0.052)	3.86	3.62 (0.52)
Genuth[35]	Far Western		5.1 (0.8)		7.12 (0.12)		3.72	
Kitabchi et al[40]	Far Western		5.6 (0.25)		7.14 (0.02)		4.34	
Lutterman et al[41]	Far Western		5.3 (1.75)		6.93 (0.09)		2.78	
Pfeifer et al[42]	Far Western		5.1 (1.0)		7.00 (0.12)		3	
Sacks et al[43]	Far Western		5.8 (0.3)		7.08 (0.05)		4.18	
Owne et al[44]	Far Western		4.2 (0.2)		7.28 (0.02)		3.78	
Adrogue et al[16]	Far Western		5.7 (1.1)		7.06 (0.11)		3.96	

(*Continued*)

Table 2 (Continued).

Authors	Region	Patient number	Reported K^+ level mean (SD/IQR)	Region-wise K^+ level mmol/L	Admission pH mean (SD/IQR)	Region-wise pH level	Calculated potassium	Regional calculated K^+ mmol/L
Umpierrez and Freire[50]	Far Western		5.4 (0.5)		7.12 (0.05)		4.02	
Newton and Raskin[52]	Far Western		4.7 (0.7)		7.23 (0.09)		3.98	
Kitabchi[57]	Far Western		5.2 (0.25)		7.11 (0.03)		3.76	
Lopes[59]	Far Western		4.7 (1.6)		7.17 (0.18)		3.62	
Robles[60]	Far Western		4.2 (0.9)		7.11 (0.15)		2.76	
Weinert[63]	Far Western		4.9 (0.7)		7.17 (0.12)		3.82	
Duhon[64]	Far Western		4.95 (n/a)		6.96 (n/a)		2.6	
Azevedo[65]	Far Western		4.9 (1.5)		7.11 (0.15)		3.46	
Talebi[21]	Far Western		5.0 (n/a)		7.19 (n/a)		4.04	

Abbreviation: K+, potassium.

value of potassium was noted at 3.4 mmol/L,[56] while the maximum was 5.8 mmol/L.[43] On average, the potassium level was 5.8 mmol/L. In a similar context, the least observed pH was 6.93[41] and the highest 7.28,[44] with an average pH being 7.13. The level of potassium after adjusting against pH ranged from 2.4–4.34 (Table 2), with an average of 3.56 mmol/L. The corresponding values for actual potassium level and pH of mentioned values was 3.4 mmol/L with a pH of 7.19,[56] and 5.6 with a pH of 7.14.[40] Thirteen included studies[38,39,41,42,51,53,60,64,65,67,68,70] calculated the value of potassium to be equal or below 3.5 mmol/L when the patients sought medical advice; out of these, only one study[56] reported the average actual potassium level to be lower than 3.5 mmol/L. Upon distributing the countries on the basis of their region, it was notable that the least potassium level was seen in mid-Eastern countries (4.4 mmol/L); the minimum pH was observed in the far-Western region (7.11); and the maximum number of patient data originated from mid-Western countries (patient number = 1,995). Nevertheless, a meta-analysis was not performed as quantitative data was not sufficient for further analysis.

Cardiovascular outcomes

Of a total of 10 studies[9,31–33,36,38,39,45,51] discussing CV outcomes, only four[21,38,39,51] reported potassium and pH, and discussed CV outcomes concurrently (Table 3). Two[31,45] of the six remaining studies neither provided pH nor potassium level in the report. The maximum number of patients reported with CV disorder in any single study was 17, where abnormal ECG was mentioned with recorded CV abnormality.[32] In the context of insulin, one death was reported secondary to an increase in insulin.[36] Interestingly, one study[9] evaluated the extent of hypokalemia in DKA and reported three deaths to myocardial infarction (MI); however, none of the deaths were attributed to hypokalemia. Only one study[33] mentioned the difference between the potassium level of alive and deceased DKA patients.

Discussion

This is the first systematic review which aims to explore CV events in patients of DKA in correlation with admission serum potassium vs pH-adjusted corrected potassium level. Moreover, it is also an attempt to signify the importance of pH-adjusted corrected potassium level in the diagnosis and management of DKA episode when weighed against the risk of CV events during an episode. In this regard, 45 studies reported admission potassium level of DKA patients and the pH-adjusted corrected potassium level was calculable for 41 studies only. However, none of the studies reported a pH-adjusted corrected potassium level and, hence, it was self-calculated to find the difference between the two values. Similarly, as for secondary outcome, 10 studies focused on the secondary outcome of a CV event in DKA, while none of the studies correlated CV outcomes with either reported or pH-adjusted corrected potassium level.

Table 3 Cardiovascular observations reported in the studies fulfilling secondary objective

Authors	Pub year	Pts (n)	Act K	pH level	Calc K	Cardiovascular notes
Baker[31]	1936	108	n/a	—	n/a	• Pulse rate above 120 bpm in 39 cases; auricular fibrillation in 3; ECG confirmed cardiac abnormality in 32 cases; circulatory collapse in 1 death • One patient with BUN above 100 mg/dL developed cardiorenal decompensation • Five deaths due to CV disease • Observation: 8 out of 11 deaths in uncomplicated coma may be attributed to CVS
Cohen et al[32]	1960	73	5.5	—	n/a	• Solutions for initial fluid replacement were made hypotonic due to elderly cardiac compensated patients • Severely acidotic patients had tachycardia • Seventeen patients had ECG abnormality which was corrected with electrolyte replacement • A patient had grade II apical systolic murmur, sino-atrial tachycardia with upper limit Q-T interval at K level of 5.0 mmol/L • Another patient recovered from myocardial failure in form of atrial fibrillation with idioventricular contractions at K level of 7.3 mmol/L; with ketosis resolved patient died of irregular rhythm, without pulse or respiration • Septic patient recovering from acidemia at 10th hour died with K value of 2.5 mmol/L; author notes hypokalemia may have contributed to death
Beigelman[33]	1971	482	5.4	—	n/a	• Mean pulse rate, accompanied by bradycardia, and diastolic BP accompanied by hypotension were lower in fatal cases • Seven acute MI patients expired, with 2 being extremely hypotensive, and 1 dying without ketosis being a contributor to death • Fatal MI patients had K level at 5.5 vs 6.5 mmol/L[1]
Page et al[36]	1974	31	5.3	—	n/a	• One patient was observed with 2 CAs and died at 10th hour of therapy; patient's insulin dose was increased and was given hydrocortisone as injection
Keller et al[38]	1975	58	5	7.00	2.9	• Six deaths were secondary to circulatory failure observed with protracted hypotension despite adequate volume replenishment and associated with severe ketoacidosis • Indescribable lower CVP was taken as a complication of severe acidemia and use of bicarbonate • One fatality was observed with increased CVP secondary to depressed cardiac activity
Asplin[39]	1975	22	4.2	7.19	3.24	• One patient suffered CA at 7th hour of admission due to pulmonary embolism
Basu et al[45]	1992	929	n/a	—	n/a	• Fourteen deaths attributed to severe metabolic distress involving CA and hyperkalemia • Seven deaths reported in patients with history of MI and three with cardiac failure • One death associated with aged patient with septicemia suffering 2 episodes of asystolic CA in conjunction with hyperkalemia • Suggestion: to confirm effect of magnesium and thrombolysis to improve DKA associated MI
Jabbar et al[51]	2004	114	4.9	7.07	3.22	• One death attributed to cardiogenic shock, while three were attributed to MI
Wong et al[9]	2015	40	4.8	—	n/a	• Despite K derangements of hypokalemia and hyperkalemia, no adverse cardiovascular outcomes were observed
Talebi et al[21]	2015	61	5	7.19	4.04	• A significant correlation is observable between hypokalemia and ECG; hypokalemia causes an increase in Q-T interval and increased resuscitation of K supplementation

Abbreviations: K, potassium; Pub, publication; Act K, actual potassium; Calc K, calculated potassium; Pts, patients; CA, cardiac arrest; ECG, Electrocardiogram; BUN, Blood urea nitrogen; CV, Cardiovascular; CVS, Cardiovascular system; BP, Blood pressure; MI, Myocardial infarction; CA, Cardiac arrest; CVP, Central venous pressure; DKA, Diabetic ketoacidosis.

The reported admission potassium level in current review was 4.91 mmol/L. Contrary to significant loss of potassium, DKA patients usually present with normal or increased potassium level, which is an established phenomenon and, hence, the observed value seems to be well within the normal range.[9,15] Moreover, most of the clinical guidelines do not suggest that potassium supplementation shall be started once the value of serum potassium is below 4.5 mmol/L.[4–7] Similarly, the mean pH-adjusted corrected potassium level observed in the current review was within the normal range of potassium level as well (3.56 mmol/L), although this value is borderline-low. However, such normo- or hyperkalemia was deceiving in nature as there were 13 studies[38,39,41,42,51,53,56,60,64,65,67,68,70] which had a corrected potassium level below 3.5 mmol/L. Further findings of the current review were in line with an aforementioned hypothesis where, in five of the studies,[38,41,56,60,64] pH-adjusted corrected potassium was as low to produce an adverse CV outcome resultant of hypokalemia.[11,15] When these studies were analyzed for any reported CV event in correlation of potassium, only three of the studies[38,39,51] reported such events; the results were, however, not in specificity to hypokalemia. The incidence of hypokalemia was very frequent in the study reported by Keller et al,[38] where 23% of DKA cases experienced a low potassium level. However, it is not mentioned whether the extent of hypokalemic episodes was associated with any of the four cases of early CV adverse outcomes or not; the authors also confirmed that these fatalities were established cases of chronic CV disease. In another study with below-normal corrected potassium level, Asplin et al did not provide any hint to the extent of hypokalemia.[39] Death was attributed to cardiac arrest 3 hours post-admission due to pulmonary embolism; however, the laboratory data of this patient seem insignificant in correlation to pH-adjusted corrected potassium. Similarly, the mean level of corrected potassium was calculated to be 3.2 mmol/L in the study by Jabbar et al.[51] Strikingly, the mortality rate was 21%, out of which five deaths were attributed to myocardial infarction (MI). No further description of post-mortem reports was provided and, hence, the link of potassium with these events remains unknown. Beside the findings above, none of the studies reported any findings related to the pH-adjusted corrected potassium level.

None of the studies reported any findings related to the pH-adjusted corrected potassium level and only one reported CV outcomes of DKA with respect to potassium.[32] It is understandable that an initial report that focused on clerking the files of DKA patients after the discovery of insulin did not focus on the potassium at all, despite adverse CV events being the reason for eight deaths in uncomplicated DKA.[31] This is because it was Holler[8] who described the effect of insulin on potassium during the treatment of DKA, which later became a part of established protocols. The attempt by Cohen et al[32] reported a detailed description of DKA admissions. The authors did report on the measured potassium level at the time of admission and also concluded for a case that hypokalemia might have been a reason for the death of a patient from septicemia. Nevertheless, any correlation between potassium level and pH was not used at the time of diagnosis.

Treatment of DKA consists of three modalities and all of these directly affect serum potassium level, ie, 1) volume resuscitation causes dilution of serum potassium concentration, 2) correction of hyperglycemia via insulin helps cellular re-entry of potassium, and 3) correction of acidosis utilizing bicarbonate causes renal clearance of potassium.[4–7] Bicarbonate is a least recommended therapeutic intervention, and a recent systematic review in this regard also did not find benefits of bicarbonate in the resolution of DKA.[75] Moreover, significance of potassium supplementation is much required crucial when bicarbonate is given with insulin. However, in the current review, there were four studies that evaluated bicarbonate in the therapy of DKA; one each by Assal et al,[34] Duhon et al,[64] Keller et al,[38] and Lutterman et al.[41] Apart from the pH-adjusted corrected potassium level for a study conducted by Assal et al[34] (3.86 mmol/L), the rest of the three studies had a very low level of corrected potassium and was calculated to be 2.9, 2.78, and 2.6 mmol/L, respectively (Table 2). Such a low level of actual potassium put the question of interest on CV profiles of patients of these studies. Notably, only Keller et al[38] reported an indescribable lower CVP which was translated as a complication of severe acidaemia and use of bicarbonate; both of these factors independently cause cardiac suppression and potassium excretion via diuresis. Neither any finding related to CV impact of DKA nor corrected potassium level has been reported in the rest of the studies. This finding of the current systematic review once again highlights the importance of adjustment of potassium with respect to acidosis so that the impact of serum potassium on CV outcomes can be dealt with in a way that further improves patient related outcomes of DKA patients.

The extent of non-adherence to the treatment protocol for the management of DKA is also a reason for hypokalemic events.[76] Abela et al[56] reported that potassium was given to the patients at a later stage of DKA resolution, with the main reasons being lack of clear instructions or secondary to not following the DKA management protocol to analyze the blood for potassium concentration; importantly, the volume of potassium resuscitation was higher and aggressive when initiated. In a similar report, a study conducted by Dhatariya et al[71] in the UK found that hypokalemia was observed in most of the patients. Additionally, non-adherence to the potassium management protocol was the highest component of deviation from treatment guidelines and observed in 20% of the cases. Moreover, as high as 67% of patients observed a value of potassium level below 4.0 mmol/L at least once during the course of hospitalization. The authors emphasized the fact that potassium replenishment, and not replacement, shall be done aggressively and insulin shall be used to maneuver the potassium level between 4.0–5.5 mmol/L. Singh et al[48] also reported similar findings when they audited the implementation of DKA treatment guidelines in the UK. In the context of adherence with the potassium resuscitation, only 30% of the cases satisfied the recommended standard of administration of potassium chloride of 70 mmol. Furthermore, 31% of the cases were found to experience hypokalemic episode incidence which was even higher when compared with events of hypoglycemia (14%). In terms of adherence to DKA treatment guidelines, nearly the same results were reported by Solá et al[54] when only 20% of the cases satisfied the potassium resuscitation criterion which resulted in a high incidence of iatrogenic hypokalemia. In another study, Wong et al[9] identify multiple entities during analyzing factors associated with non-adherence of physicians with guidelines and the event of hypokalemia. Among these were a failure to prevent, to monitor, to diagnose, and to treat hypokalemia appropriately. The study also reported that delay in initiating potassium resuscitation, inadequate amount of potassium supplementation, infrequent monitoring of potassium level, under-recognition on the hypokalemic episode, and failure to withhold insulin were the key errors which may cause an adverse event. Although the well established guidelines strongly give recommendations regarding potassium monitoring and supplementation in DKA, none of these guidelines suggest using the pH-adjusted corrected potassium level to initiate potassium resuscitation or adjust the treatment plan.[4–7] And on top of it, count to carry out the recommendations for potassium resuscitation remains very low, regardless of time, whether it is observed in the distant[9,48,54,56,71] or near past.[76] Even further, despite all the included studies in the current review that were either depicting important parameters of DKA or experimenting with its management to improve patient oriented outcomes, not a single study demonstrated the impact of potassium and acidosis on cardiovascular outcomes in DKA patients, which remains an area to explore further.

Conclusion

Potassium has an interesting outlook during the course of DKA. Despite being an intracellular ion and most affected entity throughout the development and resolution of DKA, we find that it is given the least consideration in the literature encompassing DKA. Given the extent of the current review, none of the studies in our cohort mentioned potassium in correlation with pH. It is also worthy to look into under-utilization of pH to adjust and correct the level of potassium during diagnosis and management of DKA, despite DKA patients from almost 27% of the studies experienced hypokalemia. Furthermore, most of the clinical guidelines highlight the significance of potassium supplementation during the management of DKA. However, the current review also suggests that the implementation for such supplementation is not carried out effectively. This remains a strong recommendation for healthcare professionals given that the cardiovascular outcomes are not monitored in the context of potassium and acidosis. Moreover, the features of hypokalemia are extensively observable upon an incident; the reports do not encompass potassium, pH and CV disorders simultaneously, which remains an unexplored area for reputable diabetic associations worldwide.

Strengths and limitations

Current systematic review tends to include most of the relevant scientific literature, which also encompassed the literature considered weak in terms of authenticity, or being lower in the grading of scientific criteria; hence, the results, although genuine, may not reflect light on the exact extent of the problem. Moreover, more than one third of the literature included had low quality assessment score, further weakening the suggestion provided via this systematic review. In a similar context, unavailability of the quantitative data did not allow for meta-analysis where only one of the study fulfilled three objectives

concurrently. Other than the literature quality, calculation of pH from venous and arterial blood may significantly be different for which most studies do not report the origin of sample. Similarly, although serum analysis is used mostly in a hospital setting to retrieve renal profile values, unless declared, it was not clear whether potassium was calculated using serum or plasma samples. Moreover, due to no funding of the project, the authors were not able to include non-English studies secondary to the cost of translation.

Disclosure

The authors report no conflicts of interest in regard to this work.

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