RESEARCH LETTER

Prevention of hypokalemia-induced adverse cardiovascular effects in diabetic ketoacidosis: a novel role of the pH-adjusted potassium level

Atif Usman[1], Norlaila Mustafa[2], Juman A. Dujaili[1], Mohd M. Bakry[3], Siew Hua Gan[1]

1 School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia
2 Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
3 Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Introduction Hypokalemia is a common observation in diabetic ketoacidosis (DKA) and it is usually associated with insulin deficiency.[1] At first, it hinders the inflow of serum potassium (S_K) from extra- to intracellular compartments, which triggers hyperkalemia.[2] In the course of progressive DKA, hyperglycemia and ketosis-induced osmotic diuresis increases potassium excretion, contributing to potassium depletion in intracellular compartments. Insulin deficiency–mediated increased catecholamine levels have a relative effect on potassium concentration via β-adrenoceptors.[3,4] Moreover, potassium loss is increased, as the degree of acidosis worsens.[5] Acidosis has also been associated with changes on electrocardiography similar to those typical of hypokalemia.[3,6] However, despite a significant potassium loss, patients with DKA present with various degrees of potassium disturbance on admission, which range from normal kalemia to hyperkalemia.

During DKA treatment, insulin forces S_K to shift to intracellular compartments, and the remaining S_K is diluted as a result of intravenous fluid reconstitution[1,7]; this causes clinical hypokalemia in patients with DKA. In emergency departments (EDs), this type of hypokalemia is promptly monitored using electrocardiography.[4,8] However, as this modality mainly does not reflect potassium loss in extracellular compartments, the ratio of potassium concentrations in extra- and intercellular compartments is crucial to determine hypokalemic electrocardiographic changes.[9] Therefore, much time is required to obtain a stable electrocardiogram and avoid cardiovascular risk. Considering the significance of S_K concentration, DKA treatment guidelines still recommend physicians to initiate potassium replacement if its level falls below 5.5 mmol/l[1,7,10]; such a measure puts patients at risk of hypokalemia. Contrarily, following the guidelines may put the DKA patient at risk of hyperkalemia.[11] To address the issue of timely yet safe potassium supplementation in DKA, we aimed to adjust S_K levels to the degree of acidosis (pH-adjusted potassium [pH_K] levels) as well as to evaluate the association of hypokalemic electrocardiographic changes with pH_K and other clinical parameters in DKA.

Patients and methods The data of the patients with DKA from Universiti Kebangsaan Malaysia Medical Centre, collected during 3 years (between January 2015 and December 2017) were retrospectively analyzed. Code E1X.1 (X ranging between 0 to 4) of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* was used to identify DKA cases.

Data acquisition Primary data included blood gas analysis, renal profile, complete blood count, electrocardiographic findings, and ED treatment. Secondary data provided information on demographics, physical presentation, and medical history. An electrocardiogram was considered indicative of hypokalemia when purely hypokalemic changes were reported[4,8]; multiple abnormalities on electrocardiography were regarded as unrelated to hypokalemia. With each 0.1-decrease in pH, 0.6 mmol/l was subtracted from the S_K level to obtain the pH_K level.[5]

Inclusion criteria All adult DKA patients with hyperglycemia, ketone bodies in either blood or urine, and acidosis were included in the study. Euglycemic DKA episodes were also recorded.[1] A bicarbonate level ≤18 mmol/l with pH ranging between 7.3 and 7.35 rendered the patient acidotic. Venous blood samples were adjusted by 0.3 for

Correspondence to:
Norlaila Mustafa, MD, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia, phone: +603 9145 56789, email: norlaila@ppukm.ukm.edu.my
Received: September 8, 2020.
Revision accepted: September 28, 2020.
Published online: October 5, 2020.
Pol Arch Intern Med. 2020; 130 (12): 1118-1121
doi:10.20452/pamw.15634

TABLE 1 Impact of physical and biochemical parameters as well as therapeutic procedures used in the emergency department on electrocardiographic changes associated with hypokalemia

Variable	Univariable logistic regression			Multivariable logistic regression		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Baseline characteristics						
Age	1.022	0.989–1.056	0.18	1.045	1.002–1.09	0.04
Arterial pCO_2	0.955	0.894–1.02	0.17	0.981	0.919–1.047	0.56
Sodium	0.942	0.871–1.018	0.13	0.907	0.817–1.007	0.06
pH-adjusted potassium	0.645	0.371–1.122	0.12	0.42	0.18–0.98	0.04
Therapeutic indicators						
Insulin units administered in the ED	0.678	0.462–0.995	0.047	0.581	0.368–0.918	0.02
Model summary						
R^2 (Nagelkerke)		–			0.481	
R^2 (Cox and Snell)		–			0.314	
Hosmer–Lemeshow significance		–			0.91	

Abbreviations: ED, emergency department; OR, odds ratio; pCO_2, partial pressure of carbon dioxide

pH and 0.52 mmol/l for bicarbonate to consider them as arterial blood gas values.[12]

Exclusion criteria We excluded patients with incomplete ED records in primary data, younger than 18 years of age, managed by a pediatric team, treated for gestational diabetes–induced DKA, pregnant during DKA, with a history of cardiovascular disease, admitted due to cardiovascular disease, or taking medication known to influence hypokalemic changes on electrocardiography.[8]

Statistical analysis Statistical analysis was performed using the SPSS package for social sciences, version 23 (IBM Corp., Armonk, New York,United States). Univariable logistic regression was used to determine the effect of an independent variable on the outcome, ie, hypokalemic electrocardiographic changes, with 95% CI. Variables with *P* value ≤0.2 were entered in the multivariable regression model to ascertain their strength against confounding variables. The performance of the model was recorded using a receiver operating characteristic curve, based on probabilities derived from the multiple regression model. A *P* value less than 0.05 was considered significant. Data were expressed as median and interquartile range (IQR).

Ethics The study was approved by Monash University (MUHREC-2 018-13 643), Universiti Kebangsaan Malaysia (NF-RES-2018-15), and Universiti Kebangsaan Malaysia Medical Centre (JEP--2018-145). No patient consent was required in this study.

Results

Objective observations Eighty-five patients fulfilled the inclusion criteria (Supplementary material, *Figure S1*). Median (IQR) blood glucose and ketone levels on admission were 30.9 (23.6–38.5) mmol/l and 4.3 (3–5.9) mmol/l, respectively. The study patients were moderately acidotic with median (IQR) pH at 7.22 (7–7.28) and a median (IQR) bicarbonate level of 10.7 (8.3–14.4) mmol/l. Median (IQR) white blood count and pulse rate were higher than normal, ie, 14.6×10^3/µl ($10.3–18 \times 10^3$/µl) and 108 (98–126) bpm, respectively. The remaining biochemical and physical profiles of the study patients were unremarkable.

Treatment and potassium-associated parameters The median (IQR) levels of S_K and pH_K were 4.8 (4.1–5.5) mmol/l and 3.8 (3.1–4.4) mmol/l, respectively. The study patients developed hypokalemia within a median (IQR) time of 9 (5–17) hours from admission, with a median (IQR) S_K level of 3.2 (3–3.5) mmol/l. A total of 37.6% of the patients experienced hypokalemia during pH normalization. The median (IQR) length of stay in the ED was 8 (5–14) hours, during which most patients (98.8%) received continuous intravenous insulin infusion at a median (IQR) rate of 6 (3–6) units per hour. More than 1/3 of the patients (38.8%) received potassium supplementation during their stay in the ED, according to the DKA treatment guidelines.[1,7,10]

Hypokalemic changes on electrocardiography The multivariable regression model indicated 3 variables significantly affecting hypokalemic changes on an electrocardiogram: pH_K (odds ratio [OR], 0.42; 95% CI, 0.18–0.98), units of insulin per hour (OR, 0.58; 95% CI, 0.36–0.94), and age (OR, 1.04; 95% CI, 1–1.09) (TABLE 1).

Discussion

The pH_K level showed the greatest change in the electrocardiographic pattern: with each unit decrease, chances to record a hypokalemia-induced change on an electrocardiogram increased by almost 58%. As this value is derived from pH and S_K, it was expected that both of these parameters may also influence hypokalemic electrocardiographic changes due to the pathophysiology of DKA. The initial, diminished shift of S_K from extra- to intracellular

compartments due to insulin deficiency and acidosis causes hyperkalemia in DKA.[2,3] Moreover, acidosis has an independent effect on hyperkalemia when excessive hydrogen ion buffering within cells further promotes potassium movement towards extracellular compartments.[4] Such a high S_K level can be lethal. Yet, less patients develop hyperkalemia and potassium is concurrently excreted during initial and secondary osmotic diuresis.[1] Despite these pathophysiological phenomena, the S_K level did not have any influence on our study outcome. In the context of acidosis, catecholamines directly affect the function and integrity of the cardiovascular system during the initial episode of DKA.[2,3] Although the inotropic function is maintained through the normal release of catecholamines, decreased cardiac contractility is still present depending on the degree of acidosis. The intensified inotropic and chronotropic function enhances cardiac output, thereby hindering the excessive release of catecholamines during mild episodes of acidosis, ie, at pH of 7.2 to 7.35.[2,4] With increasing acidosis in DKA, ie, at pH ≤7.2, direct cardiac suppression due to excessive hydrogen ion activity is obvious. A drop in pH reduces cardiac output and potentially increases the risk of severe shock, as cardiac tissue is sensitive to pH fluctuations and hydrogen ions cause distress to various myocardial components.[4,6] Hence, the deleterious effects of acidosis suggest that this condition may be a possible risk factor for hypokalemic changes on electrocardiography, as it affects the cardiovascular system and, concurrently, promotes hypokalemia. Although neither S_K nor pH were found to be related with hypokalemic electrocardiographic changes, pH_K was significantly associated with these changes. This finding was further advocated by the receiver operating characteristic curve (Supplementary material, *Figure S2*), which showed the area under the curve of 0.817 (95% CI, 0.71–0.93) for the probability of hypokalemic versus nonhypokalemic changes on an electrocardiogram, derived from the multiple logistic regression model.

The number of insulin units administered over an hour had the second greatest effect on hypokalemic changes on electrocardiography. In DKA, insulin affects the cardiovascular system in various ways.[2] During DKA induction, insulin deficiency increases the concentration of catecholamines and puts the cardiovascular system under hormonal stress, although the system benefits from this spike of catecholamines to compensate for lost total body water and electrolytes.[2,4] However, with decreasing blood pH and increasing breathing frequency, the cardiovascular system tends to get under stress after some time. On the other hand, insulin is also associated with the regulation of potassium levels in the body where it promotes the influx of potassium from extra- to intracellular compartments.[1,7] As a result of insulin depletion in DKA, the concentration of potassium in extracellular compartments increases.[2] Therefore, during DKA treatment, insulin is available to get potassium from extra- to intracellular compartments, thereby causing abrupt potassium loss in extracellular compartments. Besides affecting cardiovascular outcomes, insulin administration is related to the cumulative number of days of hospitalization for DKA.[7] The higher the volume of insulin administered during a given unit of time, the greater the potassium influx and, hence, a greater number of insulin units per hour precipitated hypokalemic changes on electrocardiography during a DKA episode.

Age had the weakest effect (10%) on hypokalemic electrocardiographic changes. Since diabetes is often concurrently accompanied by metabolic and cardiovascular comorbidities, these complications directly relate to cardiac dysfunction, which, in turn, may cause significant morbidity among patients. Nevertheless, a low risk of bias can be attributed to this minimal effect, as patients with a history of cardiovascular disease interfering with electrocardiographic findings were excluded from the study cohort.

To date, this is the first study on the adjustment of the S_K level to the degree of acidosis and its association with hypokalemic changes on electrocardiography in patients with DKA. Our findings reaffirmed clear hypokalemic electrocardiographic changes in patients with DKA and, for the first time, indicated that the pH_K level, rather than the S_K level, is a significant indicator of such outcome. Using pH_K as a marker of hypokalemia, it is possible to avoid hypokalemia-induced cardiac stress in patients monitored with electrocardiography and, thereby, improve overall and cardiovascular outcomes in DKA.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The authors would like to thank Tahir Mahmood Khan for his logistic support in conducting this study.

CONTRIBUTION STATEMENT The study was designed by AU, NM, and MMB. Data were retrieved and recorded by AU under the supervision of NM. The clinical aspects of the study were supervised by NM. Clinical issues were resolved by consensus between AU and NM. Data analysis was conducted by AU, JAD, and MMB. AU and SHG wrote the manuscript. The manuscript was reviewed by SHG, NM, MMB, and JAD.

CONFLICT OF INTEREST None declared.

HOW TO CITE Usman A, Mustafa N, Dujaili JA, et al. Prevention of hypokalemia-induced adverse cardiovascular effects in diabetic ketoacidosis: a novel role of the pH-adjusted potassium level. Pol Arch Intern Med. 2020; 130: 1118-1121. doi:10.20452/pamw.15634

REFERENCES

1 Kitabchi AE, Umpierrez GE, Murphy MB. Diabetic ketoacidosis and hyperosmolar state. In: DeFronzo RA, Ferrannini E, Zimmet P, Alberti G, eds.

International Textbook Of Diabetes Mellitus, 4th Edition. New Sussex, United Kingdom: John Wiley & Sons; 2015: 799-814.

2 Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. Am J Kidney Dis. 2019; 74: 682-695.

3 Long B, Warix JR, Koyfman A. Controversies in management of hyperkalemia. J Emerg Med. 2018; 55: 192-205.

4 Sheehan L, Calfas D. Cardiovascular complications of ketoacidosis. US Pharm. 2016; 41: 39-42.

5 May DB. Clinical laboratory tests. In: Shargel L, Mutnick AH, Souney PF, Swanson L, eds. Comprehensive Pharmacy Review for NAPLEX. Baltimore, Maryland, United States: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013: 542-559.

6 Kraut JA, Nagami GT. Metabolic acidosis and cardiovascular disease. In: Wesson DE, ed. Metabolic Acidosis: a Guide to Clinical Assessment and Management. New York, United States: Springer; 2016: 87-99.

7 Dhatariya KK, Umpierrez GE. Guidelines for management of diabetic ketoacidosis: time to revise? Lancet Diabetes Endo. 2017; 5: 321-323.

8 Talebi S, Ghobadi F, Cacacho A, et al. Looking at diabetic ketoacidosis through electrocardiogram window! Am J Emerg Med. 2016; 34: 263-265.

9 Udensi UK, Tchounwou PB. Potassium homeostasis, oxidative stress, and human disease. Int J Clin Exp Physiol. 2017; 4: 111-122.

10 Cieluch A, Uruska A, Falkowski B, et al. Nonadherence to potassium replacement protocol leads to prolonged management of diabetic ketoacidosis. Pol Arch Intern Med. 2018; 128: 416-420.

11 Venkatesh B, Pilcher D, Prins J, et al. Incidence and outcome of adults with diabetic ketoacidosis admitted to ICUs in Australia and New Zealand. Crit Care. 2015; 19: 451.

12 Middleton P, Kelly AM, Brown J, Robertson M. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. Emerg Med J. 2006; 23: 622-624.