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

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Article type: Research letter

Received: September 8, 2020.

Accepted: September 28, 2020.

Published online: October 5, 2020.

ISSN: 1897-9483
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Short title: Acidosis and Potassium in DKA: CV Outcomes

Conflict of interest: None declared.
Prevention of Hypokalemia Induced Adverse Cardiovascular Effects in Diabetic Ketoacidosis: Novel Role of pH-adjusted Potassium

BACKGROUND

Hypokalemia is a common observation in diabetic ketoacidosis (DKA), and is usually tied with lack of insulin [1]. At first, it hinders influx of serum-potassium ($S_K$) from extracellular (ECF) to intracellular (ICF) compartment triggering hyperkalemia [2]. With progress of DKA, hyperglycemia and ketosis-induced osmotic diuresis increases potassium excretion depleting ICF potassium. Lack-of-insulin mediated increased catecholamines have relative effect on potassium via beta-adrenoceptor activity [3,4]. Moreover, loss of potassium is exacerbated as the degree of acidosis worsens [5]. In this regard, it is also known that acidosis leads to similar changes in electrocardiogram (ECG) as of hypokalemia [3,6]. However, despite significant loss, DKA patients range between eukalemia to hyperkalemia at admission.

With commencement of DKA treatment, insulin forces $S_K$ to shift to ICF and intravenous (IV) fluid reconstitution dilutes remaining $S_K$ [1,7]; this causes clinical hypokalemia in DKA patients. In emergency-department (ED), such hypokalemia is promptly monitored via ECG [4,8]. However, as ECG mainly does not reflect the loss of ECF potassium, ratio of ECF to ICF potassium is important to determine hypokalemic-ECG changes [9]. Therefore, much time is required to achieve stable ECG and avoid cardiovascular (CV) risks. Considering $S_K$ criticality, DKA treatment guidelines still recommend to initiate potassium resuscitation if its level falls below 5.5mmol/L [1,7,10]; such measure places patients at risk of hypokalemia. Contrarily, following the guidelines may put the DKA patient at risk of hyperkalemia [11]. To address issue of timely yet safe potassium supplementation in DKA, we aimed to adjust
$S_K$ with degree of acidosis (pH-adjusted potassium) ($pH_K$), and evaluate association of hypokalemic-ECG changes with $pH_K$ and other clinical parameters of DKA.

**METHODOLOGY**

Three-years (January-2015 to December-2017) data of DKA patients from Universiti Kebangsaan Malaysia Medical Centre (UKMMC) were retrospectively reviewed. Code E1X.1 of International classification of diseases-v.10 was used to locate DKA cases (“X” ranges 0–4).

*Data acquisition*

Primary data included blood-gas analysis, renal profile, complete blood count, ECG and ED treatment. Secondary data comprised of demographics, physical presentation, and clinical history. An ECG was considered indicating hypokalemia when purely hypokalemic changes were reported [4,8]; an ECG recording multiple anomalies was labelled non-hypokalemic-ECG change. With each 0.1 decrease in pH, 0.6mmol/L was subtracted from $S_K$ to acquire $pH_K$ [5].

*Inclusion criteria*

All adult patients experiencing DKA with recorded hyperglycemia, ketones-bodies in either blood or urine, and acidosis were included. Euglycemic DKA episodes were also recorded [1]. Bicarbonate level of $\leq 18$mmol/L with pH ranging between 7.30–7.35 rendered patient acidic. Venous blood samples were adjusted by 0.3 for pH and 0.52mmol/L for bicarbonate to consider them as arterial blood-gas values [12].

*Exclusion criteria*

Cases were excluded if they had incomplete ED record on primary data; had age below 18-years; were managed by pediatric team, were treated for gestational diabetes induced DKA,
were pregnant during DKA; had history of CV disorder, were admitted due to CV disease, or were taking medicine known to influence hypokalemic-ECG changes [8].

Statistical analysis

Univariable logistic regression was used via Statistical package for social sciences (SPSS) v.23 to identify effect of independent variable on outcome measure, i.e. hypokalemic-ECG changes, with confidence interval of 95%. Variables having a \( P \)-value ≤0.200 were forwarded to multivariable regression model to ascertain its strength against confounding variables. Performance of the model was recorded using a receiver operating characteristic (ROC) curve utilizing derived probabilities from multiple regression model. A \( P \)-value <0.05 rendered the variable to be significantly influencing the outcome of interest. The data were expressed as median and interquartile-range (IQR).

Ethics

The study was ethically approved by Monash University (MUHREC-2018-13643), Universiti Kebangsaan Malaysia (NF-RES-2018-15), and UKMMC (JEP-2018-145). Consent to participate was not applicable in this study.

RESULTS

Objective observations

Eighty-five patients fulfilled inclusion criteria (supplementary material). Median blood glucose and ketones levels on admission were 30.9mmol/L (23.6–38.5) and 4.3mmol/L (3.0–5.9), respectively. The patients were moderately acidotic with pH at 7.22 (7.00–7.28) and bicarbonate at 10.7mmol/L (8.3–14.4). Among general profiles, white blood count and pulse rate were higher than normal, i.e. 14.6x10³/µL (10.3–18.0) and 108 (98–126), respectively. Remaining biochemical and physical profiles of the patients were unremarkable.
**Treatment and potassium-associated parameters**

Median levels of $S_K$ and $pH_K$ were 4.8 (4.1–5.5) and 3.8mmol/L (3.1–4.4), respectively. Patients experienced hypokalemia within 9.0 hours (5–17) from admission with $S_K$ level at 3.2mmol/L (3.0–3.5). 37.6% patients suffered hypokalemia during pH-normalization. Length-of-stay in ED was 8 hours (5–14) during which, most (98.8%) patients received continuous IV insulin at a rate of 6 units per hour (3.0–6.0). More than one-third (38.8%) patients received potassium supplementation according to DKA treatment guidelines during the length-of-stay at ED [1,7,10].

**Hypokalemic-ECG changes**

Multivariable regression model forwarded three variables significantly affecting hypokalemic-ECG changes; $pH_K$ (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: 1.00-1.09) (Table 1).

**DISCUSSION**

The $pH_K$ showed highest change in the ECG pattern where with each unit decrease, chances to acquire hypokalemia-prone ECG difference increased by almost 58%. As it is derived from pH and $S_K$, it was expected that both of these may also influence the hypokalemic-ECG changes due to pathophysiology of DKA. Initial diminished ECF to ICF shift of $S_K$ due to lack of insulin 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 ECF [4]. The effects of such high $S_K$ can produce lethal effects. Yet, less patients experience hyperkalemia as excretion of potassium is concurrently being carried out by initial and secondary osmotic diuresis [1]. Despite these pathophysiological phenomena, the $S_K$ level did not have any influence on outcome measure. In context of acidosis, catecholamines directly affect the CV-system’s (CVS) functionality
and integrity during initial episode of DKA [2,3]. Although inotropic function is maintained via normal release of catecholamines, depression of cardiac contractility is still present depending upon degree of acidosis. Augmented inotropic and chronotropic function enhances cardiac output thereby hindering the excessive release of catecholamines during mild episodes of acidosis i.e. pH 7.2-7.35 [2-4]. With increase in degree of acidosis in DKA, i.e. pH ≤7.2, direct cardiac suppression due to excessive hydrogen ions is obvious. Drop in pH reduces cardiac output and potentially increases the risk of severe shock as cardiac tissue is sensitive to pH fluctuation, where hydrogen ions cause distress to various myocardial components [4,6]. Hence, the deleterious effects of acidosis renders it a possible factor for hypokalemic-ECG change as it affects CVS and promotes hypokalemia concurrently. In this regard, though neither S_K nor pH were found to be related with hypokalemic-ECG changes, the pH_K had significant association with these changes. This notion was further advocated by ROC curve (supplementary material) where probabilities towards hypokalemic versus non-hypokalemic-ECG changes driven from multiple logistic regression model had AUC of 81.7%; (95% CI 0.71-0.93).

Units of insulin given over an hour had second highest influence on hypokalemic-ECG changes. Effects of insulin on CVS are diverse in DKA [2]. During DKA induction, lack of insulin increases concentration of catecholamines resultantly putting CVS under hormonal stress, though the CVS benefits from this spike of catechoamines to compensate for loss of total body water and electrolytes [2,4]. However, with decrease in blood pH and increase in breathing frequency, CVS tends to get under stress over the time. On the other hand, insulin is also associated with regulation of potassium concentration in the body where it promotes the influx of potassium from ECF to ICF [1,7]. As a result of insulin depletion in DKA, concentration of potassium in ECF increases [2]. Therefore, with commencement of DKA treatment, insulin is readily available to get ECF potassium to ICF thereby causing abrupt
disappearance of ECF potassium. Beside CV outcomes, insulin itself is related with cumulative days of hospitalization in DKA as well [7]. In this regard, higher the volume of insulin during a unit of time, higher will be the potassium influx and hence, it is understandable that insulin units per hour precipitated hypokalemic-ECG changes during a DKA episode.

Least weighed effect (10%) on hypokalemic-ECG changes was depicted by age. Since diabetes mellitus attracts other diseases which encompass metabolic and CV continuum with passage of time, these complication directly relate to cardiac dysfunction which may in turn cause significant morbidity to the patients. Nevertheless, a small risk of bias may be attributed to this minimal effect; the patients having active history of ECG interfering CV disorder were excluded from current cohort.

To date, this is the first study observing adjustment of $S_K$ with degree of acidosis, and its association with hypokalemic-ECG changes in patients of DKA. Our findings reaffirm pure hypokalemic-ECG changes in DKA patients and, for the first time, indicate that the $pH_K$ is a significant indicator of such outcome measure rather than $S_K$. By utilizing $pH_K$ as a marker of hypokalemia, it is possible to avoid hypokalemia-induced cardiac stress when monitored via ECG thereby improving patient and CV outcomes of DKA patients.
**Acknowledgement**

Authors are pleased to acknowledge Tahir Mahmood Khan for his logistic support to conduct this study.

**Authors' contributions**

Study was designed by AU, NM and MMB. Data retrieval and recording were done by AU under supervision of NM. Clinical aspects of study were supervised by NM. Clinical conflicts were resolved by discussion between AU and NM. Data analysis was agreed upon by AU, JAD and MMB. Manuscript was written by AU and SHG. Manuscript was reviewed by SHG, NM, MMB and JAD.
REFERENCES


Table 1: Impact of physical and biochemical parameters, and emergency-department therapeutic measures on electrocardiogram changes attributed to hypokalemia.

<table>
<thead>
<tr>
<th>Variate</th>
<th>Univariable Logistic Regression</th>
<th>Multivariable Logistic Regression</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Presenting profiles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.022</td>
<td>0.989, 1.056</td>
</tr>
<tr>
<td>Arterial pCO₂</td>
<td>0.955</td>
<td>0.894, 1.020</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.942</td>
<td>0.871, 1.018</td>
</tr>
<tr>
<td>pH-adjusted potassium</td>
<td>0.645</td>
<td>0.371, 1.122</td>
</tr>
<tr>
<td><strong>Therapeutic indicators</strong></td>
<td></td>
<td></td>
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<tr>
<td>ED insulin units</td>
<td>0.678</td>
<td>0.462, 0.995</td>
</tr>
<tr>
<td><strong>Model Summery</strong></td>
<td></td>
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<tr>
<td>$R^2$ (Nagelkerke)</td>
<td></td>
<td></td>
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<tr>
<td>$R^2$ (Cox &amp; Snell)</td>
<td></td>
<td></td>
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<tr>
<td>HL significance</td>
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</tbody>
</table>

OR: Odds ratio; CI: Confidence interval; mmol/L: millimoles/Liter; ED: Emergency-department; pCO2: Partial pressure of carbon dioxide; HL: Hosmer Lemeshow
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>CVS</td>
<td>Cardiovascular system</td>
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<tr>
<td>DKA</td>
<td>Diabetic ketoacidosis</td>
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<tr>
<td>ECF</td>
<td>Extracellular fluid</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>ICD</td>
<td>International classification of diseases</td>
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<tr>
<td>ICF</td>
<td>Intracellular fluid</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<td>mmol/L</td>
<td>millimole/liter</td>
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<tr>
<td>PCO₂</td>
<td>partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operatince characteristic</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical package of social sciences</td>
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