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ORIGINAL ARTICLE

Interference of ketone bodies on laboratory creatinine measurement in children with DKA: a call for change in testing practices

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Abstract

Background The presence of ketone bodies (KBs) can interfere with creatinine (Cr) measurement in both enzymatic and Jaffe methods. Since a high proportion of children hospitalized for diabetic ketoacidosis (DKA) develop acute kidney injury (AKI), here we investigate whether KB interferences affect the accuracy of pediatric Cr measurement.

Methods Residual patient plasma samples were pooled to make three Cr levels (~50, 100, and 250 μM). KBs (acetone, acetoacetate, and β-hydroxybutyrate) were used to spike the pooled samples. All samples were measured for Cr by two enzymatic methods (E1 and E2), two Jaffe methods (J1 and J2), and LC–MS/MS. LC–MS/MS was considered the gold standard, and the % difference in Cr concentration was calculated for each method.

Results E1 and E2 were unaffected by the presence of all three KBs. J1 and J2 were unaffected by the presence of β-hydroxybutyrate. The presence of acetone resulted in dose-dependent positive interference in both Jaffe methods, whereas the presence of acetoacetate resulted in dose-dependent positive and negative interference in J1 and J2, respectively.

Conclusions Compared to the enzymatic methods, the Jaffe methods were much more susceptible to interference by acetone and acetoacetate, especially at lower Cr values which are commonly seen in pediatrics. Interpretation of changes in Cr concentration between different hospitals when transferring patients can become ambiguous and true kidney function unclear if different methods are used without awareness of method-specific biases. To improve DKA patient care, we recommend standardizing all of the Cr methods to an enzymatic method.

Keywords Diabetic ketoacidosis · Acute kidney injury · Ketone bodies · Creatinine · Jaffe method · Enzymatic method

Abbreviations

DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
KB	Ketone bodies
Ac	Acetone
AA	Acetoacetate
β-OHB	β-Hydroxybutyrate
AKI	Acute kidney injury
Cr	Serum creatinine
LC–MS/MS	Liquid chromatography-tandem mass spectrometry
E1	Ortho VITROS® 5600
E2	Roche cobas® C501
J1	Beckman Coulter UniCel DxC 800
J2	Siemens VISTA® 1500
KDIGO	The Kidney Disease: Improving Global Outcomes

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Introduction

Diabetic ketoacidosis (DKA) is characterized by insulin deficiency, hyperglycemia, metabolic acidosis, and the production of ketone bodies (KBs) such as acetone, acetoacetate, and β-hydroxybutyrate (β-OHB). Recent reports have indicated that 30–64.2% of children hospitalized for DKA

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develop acute kidney injury (AKI) [1–3], highlighting the importance of accurate diagnosis and follow-up testing. The diagnosis and staging of AKI include the measurement of serum creatinine (Cr). However, the presence of KBs has been reported to interfere with Cr measurement in both enzymatic and Jaffe methods leading to falsely high and falsely low results, with less interference observed in enzymatic methods [4–8]. Although many pediatric hospitals use enzymatic methods, general hospitals tend to rely on Jaffe methods due to their lower costs. This presents a particular challenge for clinicians as children with diabetes mellitus may access care for DKA at multiple sites throughout their disease course, with the potential for Cr measurements on different instruments using Jaffe or enzymatic methodology with varying KB interference profiles.

To investigate the potential KB interference profiles in our region, especially with newer model laboratory analyzers, we undertook a multi-center study using pooled patient plasma samples spiked with KBs to assess the accuracy of two enzymatic and two Jaffe methods in comparison to the gold standard, liquid chromatography-tandem mass spectrometry (LC–MS/MS).

Methods

Lithium acetoacetate and DL-β-hydroxybutyric acid sodium salt were purchased from Sigma-Aldrich Canada. Acetone was purchased from Fisher Chemical. Pooled patient plasma samples were prepared at Cr concentrations of approximately 50, 100, and 250 µM. For each Cr concentration, zero pools and high pools of 50 mM acetone, 20 mM acetoacetate, and 20 mM β-OHB were prepared. The zero pools and high pools were then mixed in the requisite proportions to make final concentrations of 0, 12.5, 25, 37.5, and 50 mM acetone; 0, 5, 10, 15, and 20 mM acetoacetate; and 0, 5, 10, 15, and 20 mM β-OHB [5, 7, 8]. The samples were then split into five aliquots and distributed to each center where they were tested by either one of two enzymatic assays, VITROS® 5600 (Ortho Clinical Diagnostics, E1) or cobas® C501 (Roche Diagnostics, E2), or one of two Jaffe methods, UniCel DxC 800 (Beckman Coulter, J1) or VISTA® 1500 (Siemens Healthcare Limited, J2), or Xevo TQ MS LC–MS/MS (Waters Corporation) in duplicate. This multicenter experimental in vitro study utilized instruments at one pediatric tertiary care hospital and three general teaching hospitals. Data was analyzed using Excel (Microsoft) and Prism version 8 (GraphPad).

Both enzymatic and Jaffe methods are based on colorimetry, in which Cr concentration is proportional to absorbance. In the enzymatic assays, E1 and E2, Cr reacts in multiple enzymatic steps before reacting with a dye for quantification. In the Jaffe methods, J1 and J2, Cr reacts directly with alkaline picrate to produce a colored complex. Compared to J1, J2 incorporates a two-point reading of the reaction to reduce interferences. LC–MS/MS detects Cr by sequentially isolating the initial intact Cr ion and then after collision-induced dissociation further isolating a fragment ion. The LC–MS/MS method utilized for this study was developed and validated with reference to a prior report [6]. The accuracy of Cr measurements by all the analytical instruments utilized was confirmed with Cr proficiency testing material from the College of American Pathologists (CAP). The % difference from the LC–MS/MS-determined Cr concentration was calculated for each condition in each method. Interference was defined as exceeding ± 15%, which is the error allowed for Cr defined by CAP and other expert groups. Institutional review board approval was waived for this quality improvement project.

To assess the different Cr methods used in our region, we conducted a survey of all 107 laboratories in British Columbia. This survey was in collaboration with the proficiency testing program, Canadian External Quality Assessment Laboratory (CEQAL). This regional accuracy-based proficiency testing program was adopted in 2008 to support the standardization of Cr and eGFR reporting so laboratories in our region could compare their results [9].

Results

E1 and E2 were largely unaffected by the presence of KBs, as the absolute % biases relative to the Cr levels by LC–MS/MS were < 15% (Table 1 indicating highest KB exposures tested; range from – 12 to 8%). Similarly, J1 and J2 were largely unaffected by the presence of 20 mM β-OHB (Table 1, range from – 10 to – 1%). Linear regression analysis was performed using observed Cr concentrations in the presence of varying concentrations of KBs, and the slope deviances from zero were determined (Fig. 1). The presence of acetone resulted in highly significant (*P*-value range, $P < 0.01$ to $P < 0.0001$) dose-dependent positive interference in both Jaffe methods, whereas the presence of acetoacetate resulted in highly significant (*P*-value range, $P < 0.01$ to $P < 0.0001$) dose-dependent positive and negative interference in J1 and J2, respectively (Fig. 1). The magnitude of interference by acetone and acetoacetate in J1 and J2 was inversely proportional to the Cr concentration, with the largest interferences observed at lower Cr values (Table 1). In the presence of the lowest concentration of acetone (12.5 mM), 40.2 µM of Cr by LC–MS/MS became 61 µM by J1 (52% increase) and 70 µM by J2 (74% increase); and 97.5 µM of Cr by LC–MS/MS became 112 µM by J1 (15% increase) and 122 µM by J2 (25% increase), respectively. In the presence of the lowest concentration of acetoacetate (5 mM), 39.3 µM of Cr by LC–MS/MS became 64 µM by J1 (63% increase) and

Table 1 Maximum bias from liquid chromatography-tandem mass spectrometry observed on the enzymatic and Jaffe methods

KB	[Cr] by LC–MS/MS (μM)	[Cr] (μM) (% bias)			
		E1	E2	J1	J2
50 mM Ac	38.1	39 (2%)	41 (8%)	138 (262%)	162 (325%)
	94.6	90 (−5%)	90 (−5%)	191 (102%)	209 (121%)
	243.5	228 (−6%)	218 (−10%)	324 (33%)	338 (39%)
20 mM AA					
	40.5	40 (−1%)	40 (−1%)	137 (238%)	13 (−68%)
	100.2	91 (−9%)	88 (−12%)	181 (81%)	59 (−41%)
	231.8	230 (−1%)	217 (−6%)	318 (37%)	179 (−23%)
20 mM β-OHB					
	42.3	43 (2%)	40 (−5%)	42 (−1%)	39 (−8%)
	97.1	93 (−4%)	87 (−10%)	89 (−8%)	87 (−10%)
	239.4	234 (−2%)	218 (−9%)	222 (−7%)	220 (−8%)

KB, ketone body; *Cr*, serum creatinine; *LC–MS/MS*, liquid chromatography-tandem mass spectrometry; *E1*, Ortho VITROS® 5600; *E2*, Roche cobas® C501; *J1*, Beckman Coulter UniCel DxC 800; *J2*, Siemens VISTA® 1500; *Ac*, acetone; *AA*, acetoacetate; *β-OHB*, β-hydroxybutyrate

36 μM by J2 (8% decrease); and 98.4 μM of Cr by LC–MS/MS became 116 μM by J1 (18% increase) and 84 μM by J2 (15% decrease), respectively (Table 2). Linear regression analysis was performed and significant slope deviance from zero is indicated by the following: $*P<0.05$; $**P<0.01$; $***P<0.001$; $****P<0.0001$.

The results of the Cr methodology survey in our region are summarized in Table 3. There are five major laboratory analyzers used in British Columbia: Ortho, Beckman Coulter, Siemens, Abbott, and Roche. Some manufacturers can offer both enzymatic and Jaffe Cr methods, while others offer only one type of method.

Discussions

Consistent with previous reports [4, 5, 7, 8], the Jaffe methods investigated here were highly susceptible to interference by acetone and acetoacetate. The magnitude of interference was the largest at lower Cr values, which are concentrations commonly seen in the pediatric population. Therefore, KB interferences may complicate the assessment of kidney function and clinical management when pediatric patients access care for DKA at different centers. Hursh et al. reported that the incidence of AKI in children with DKA at BC Children's Hospital (BCCH) was 64.2% [1]. Of pediatric DKA admissions to BCCH, 54.5% had initially presented at general hospitals and among these, 74.6% were diagnosed with AKI [1]. In contrast, the percentage of AKI for the children who presented to the Emergency Department of BCCH directly was only 25.4% [1]. The higher percentage of AKI in children who were transferred from general hospitals may be partly due to the Cr measurements with Jaffe methods in our region which were affected by KB interference, as we have demonstrated here.

Based on The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, AKI is defined as any of the following: increase in Cr by ≥ 26.5 μM within 48 h; increase in Cr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 h [10]. Therefore, the Cr value alone plays a major role in the diagnosis and staging of AKI. This is especially true in children because tracking hourly urine output is unreliable [1]. Since baseline Cr values were not available for children who presented with DKA, calculation of baseline Cr with the Schwartz equation [11] was applied in pediatric DKA studies [1–3]. There are two creatinine-based Schwartz equations for estimating GFR: Schwartz equation for enzymatic Cr methods and Schwartz equation for Jaffe Cr methods. The difference between these two equations is a larger constant in the Schwartz equation for Jaffe Cr methods, which reflects the lower Cr values by enzymatic methods, especially at low levels of Cr [11]. Although the use of enzymatic Cr methods in pediatric hospital laboratories has been standard practice for over 10 years since the study published by Cobbaert et al. [12], most general hospital laboratories still rely on Jaffe methods. Without the knowledge of different Cr methods (based on the normal GFR of 120 ml/min/1.73 m^2) used in various laboratories, pediatricians may use the Schwartz equation for enzymatic Cr methods to estimate the baseline Cr for children who presented to general hospitals using Jaffe Cr methods. This would lead to an underestimation of baseline Cr and an overdiagnosis of AKI in children with DKA.

KBs are produced in the liver, with acetoacetate and β-OHB being the predominant molecules, and acetone being produced by spontaneous decarboxylation of acetoacetate

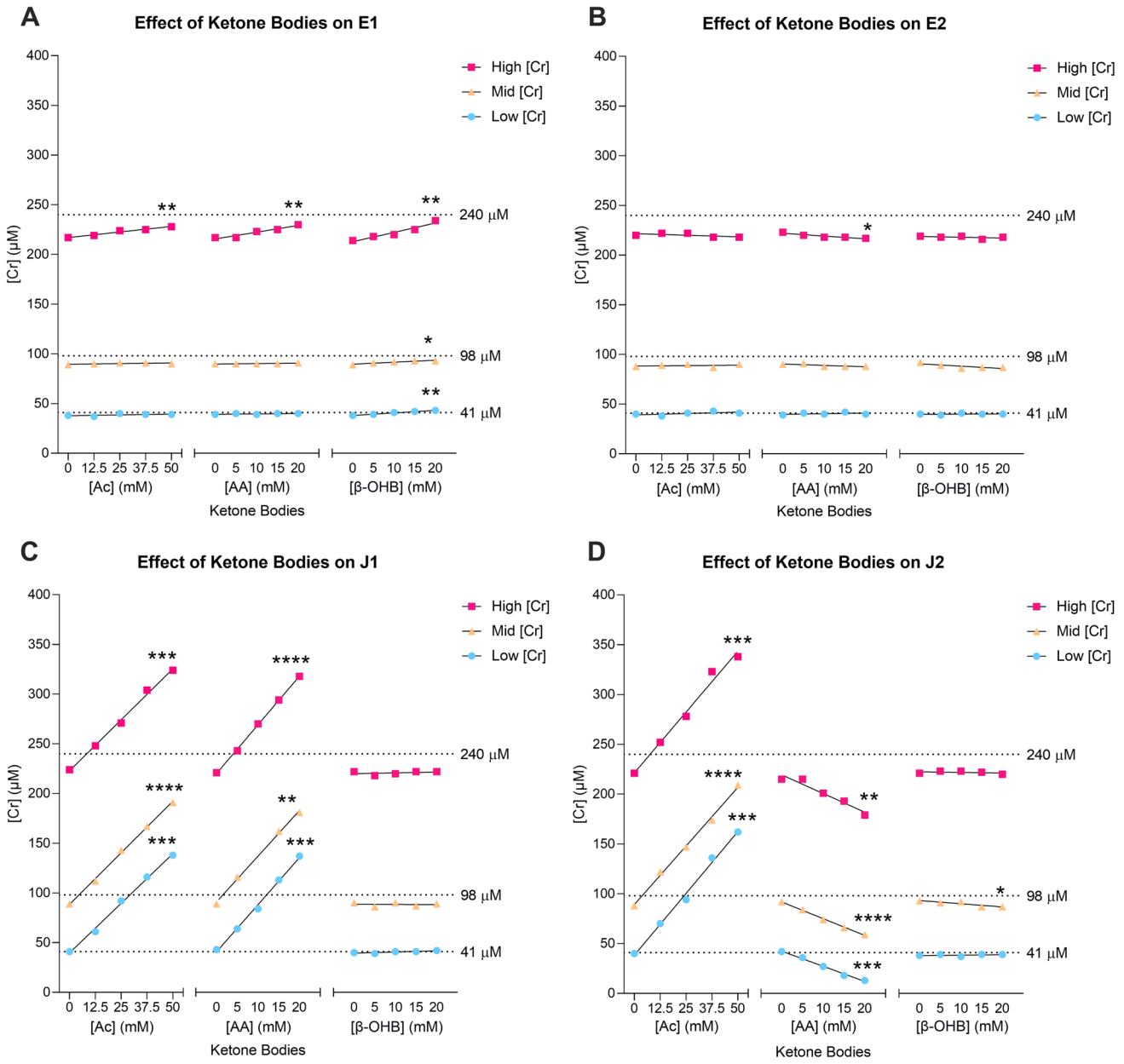

Fig. 1 Acetone and acetoacetate highly interfere with Cr measurement by two Jaffe methods. The dotted lines indicate average Cr concentration by LC–MS/MS without KBs. In the presence of the lowest concentration of acetone (12.5 mM), Cr of 40.2 μM by LC–MS/MS became 61 μM by J1 (52% increase) and 70 μM by J2 (74% increase). In the presence of the lowest concentration of acetoacetate (5 mM), Cr of 39.3 μM by LC–MS/MS became 64 μM by J1 (63% increase) and 36 μM by J2 (8% decrease). Linear regression analysis was performed and significant slope deviance from zero is indicated by the following: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$

[13, 14]. The lowest concentration of acetoacetate investigated here (5 mM) was similar to the in vivo concentration (1.3–5.1 mM) investigated in the study by Kemperman et al. [4]. Interestingly, the median concentration of β-OHB was 5.1 mmol/l in Kemperman's study which was almost half of the concentration seen in the Hursh et al. study (10.1 mM), illustrating higher levels of KBs are seen in children with DKA. A search of our laboratory information system identified that the highest concentration of β-OHB in children reported by our lab was 17 mM. In our study, the positive bias by J1 of 5 mM of acetoacetate concentration was greater than 50%, which would be diagnostic of stage 1 AKI based on Cr values alone. Similarly, the lowest concentration of acetone investigated here (12.5 mM) was within the range reported by Sulway et al. (2.5–12.9 mM) in patients with DKA [15]. This illustrates that the positive bias

Table 2 Minimum bias from liquid chromatography-tandem mass spectrometry observed on the enzymatic and Jaffe methods

KB	[Cr] by LC–MS/MS (μM)	[Cr] (μM) (% bias)			
		E1	E2	J1	J2
12.5 mM Ac	40.2	37 (−8%)	39 (−5%)	61 (52%)	70 (74%)
	97.5	90 (−8%)	89 (−9%)	112 (15%)	122 (25%)
	236.1	219 (−7%)	222 (−6%)	248 (5%)	252 (7%)
5 mM AA	39.3	40 (2%)	41 (4%)	64 (63%)	36 (−8%)
	98.4	90 (−9%)	91 (−8%)	116 (18%)	84 (−15%)
	234.2	217 (−7%)	220 (−6%)	243 (4%)	215 (−8%)
5 mM β-OHB	44.6	39 (−13%)	39 (−13%)	39 (−13%)	39 (−13%)
	101.3	91 (−10%)	89 (−12%)	86 (−15%)	91 (−10%)
	245.9	218 (−11%)	218 (−11%)	218 (−11%)	223 (−9%)

KB, ketone body; *Cr*, serum creatinine; *LC–MS/MS*, liquid chromatography-tandem mass spectrometry; *E1*, Ortho VITROS® 5600; *E2*, Roche cobas® C501; *J1*, Beckman Coulter UniCel DxC 800; *J2*, Siemens VISTA® 1500; *Ac*, acetone; *AA*, acetoacetate; *β-OHB*, β-hydroxybutyrate

Table 3 Creatinine methodology survey in British Columbia

Method	Manufacturer	Number of laboratories
Enzymatic	Roche	27
	Ortho	30
	Abbott	9
Total number of enzymatic methods		66
Jaffe	Beckman Coulter	31
	Siemens	9
	Roche	1
Total number of Jaffe methods		41
Total number of Cr methods in British Columbia		107

Cr, serum creatinine

of 12.5 mM of acetone by J1 and J2 on Cr concentrations commonly seen in pediatrics would also meet the diagnostic criteria for AKI. The interference by acetone and acetoacetate becomes smaller as the Cr concentration increases. This likely explains why the discrepancy in adult patients, who have higher Cr concentrations, may not be noticed. The level of acetone in blood has been found to be greater than acetoacetate in established ketoacidosis [15, 16], and after treatment, acetone remained elevated for periods of up to 42 h [15]. Considering the dynamic flux among the three KBs in patients with DKA, the combined interference profiles on Cr values by Jaffe methods are difficult to estimate, especially as acetoacetate interference on J1 and J2 was observed to be in opposite directions. If the results of different methods are compared without awareness of method-specific biases, interpreting changes in Cr concentration can be ambiguous. In these cases, true kidney function can be unclear, which may lead to inaccurate diagnosis and disease staging, even followed by unnecessary admission to the ICU. Potential interference from KBs on Cr values should also be taken into consideration when designing and reporting clinical studies. Reporting the frequency and stage of AKI without discussing the methodology used to measure Cr can make true kidney function unclear [1–3, 13].

The Cr methodology survey in our region demonstrated that 41 out of 107 (38.3%) laboratories still use Jaffe Cr methods. Furthermore, according to the Chemistry/Therapeutic Drug Monitoring C-A 2020 Participant Summary, Jaffe Cr methods are still used in approximately two-thirds of the laboratories among over 5000 participating sites. Children with DKA who presented to general hospitals that still use Jaffe methods could be inaccurately diagnosed with an AKI due to KB interferences in combination with the underestimation of baseline Cr with the Schwartz equation for enzymatic Cr methods. These children could potentially have an inaccurate diagnosis of AKI before their transfer to pediatric centers, where enzymatic Cr methods have been commonplace for the last two decades. In addition, the rapid normalization of kidney function seen in the pediatric population in the study by Martinez Herrada et al. could be attributable to a narrowing in the difference between the actual and factitious Cr levels associated with a decrease in KBs that occur in the course of treatment [17].

Other than KBs, substances such as bilirubin, hemoglobin, proteins, and drugs including phenytoin, cephalosporins, and aminoglycosides also cause more significant interference in Jaffe methods than enzymatic methods [5, 6, 9, 18, 19]. Although Cr reporting bias has been reduced in recent years by standardizing calibrators to isotope dilution mass spectrometry, these developments do not eliminate the analytical variations and interferences in Jaffe methods. Significant interlaboratory variability in Cr measurement still exists [20, 21], and the variability is even higher in samples with interfering substances [9]. An inaccurate diagnosis of worsening kidney function concluded from elevated Cr values caused by analytical variations and interferences can

lead to unnecessary investigations, including repeat serum Cr measurements, imaging, and even kidney biopsy. Therefore, the analytical variability in Jaffe Cr methods in terms of bias, imprecision, and lack of specificity had previously questioned the clinical utility of Jaffe Cr methods [21, 22]. For the accurate assessment of kidney function, especially in patients with DKA, AKI, or kidney transplant, it is the ideal time for widespread use of enzymatic methods in general hospitals.

Conclusion

Our work informs the clinical community of the challenges that can be encountered when Jaffe methods are used in hospitals that care for patients with DKA. Strategies to alleviate this ambiguity and provide the best quality of care include increasing the awareness of the KB interference profiles of different laboratories, indicating when Cr is determined by Jaffe methods in patients with DKA, and standardizing all of the Cr methods to an enzymatic method. The primary limitation of this study was the use of pooled patient plasma samples. Future prospective studies with simultaneous measurements of Cr by both enzymatic and Jaffe methods in children with DKA are needed.

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Author contribution Dr. Wang conceptualized and designed the study (principal investigator). All the authors contributed to data acquisition, analysis, and interpretation. Statistical analysis was performed by Mr. Feldman-Kiss and Dr. Dubland. Mr. Feldman-Kiss, Dr. Dubland, and Dr. Wang drafted the manuscript. All the authors contributed to critical revisions of the manuscript for intellectual content and agreed to be guarantors of the work. Administrative, technical, and material support was provided by Drs. Dubland, Li, Sinclair, and Cleve.

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Data availability Available.

Code availability Not applicable.

Declarations

Ethics approval Waived by the ethics board of University of British Columbia.

Consent to participate Not applicable.

Consent for publication Yes.

Conflict of interest The authors declare no competing interests.

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