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Short Communication

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Relationships among biochemical measures in children with diabetic ketoacidosis

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Abstract

Objectives: Investigating empirical relationships among laboratory measures in children with diabetic ketoacidosis (DKA) can provide insights into physiological alterations occurring during DKA. We determined whether alterations in laboratory measures during DKA conform to theoretical predictions.

Methods: We used Pearson correlation statistics and linear regression to investigate correlations between blood glucose, electrolytes, pH and PCO_2 at emergency department presentation in 1,681 pediatric DKA episodes. Among children with repeat DKA episodes, we also assessed correlations between laboratory measures at the first vs. second episode.

Results: pH and bicarbonate levels were strongly correlated (r=0.64), however, pH and PCO_2 were only loosely correlated (r=0.17). Glucose levels were correlated with indicators of dehydration and kidney function (blood urea nitrogen (BUN), r=0.44; creatinine, r=0.42; glucose-corrected sodium, r=0.32). Among children with repeat DKA episodes, PCO_2 levels tended to be similar at the first vs. second episode (r=0.34), although pH levels were only loosely correlated (r=0.19).

Conclusions: Elevated glucose levels at DKA presentation largely reflect alterations in glomerular filtration rate. pH and PCO_2 are weakly correlated suggesting that respiratory responses to acidosis vary among individuals and may be

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influenced by pulmonary and central nervous system effects of DKA.

Keywords: acid-base balance; diabetes; diabetic ketoacidosis; electrolytes.

Children with diabetic ketoacidosis (DKA) present with biochemical alterations including hyperglycemia, acidosis, hypocapnia and electrolyte abnormalities. The severity of these biochemical derangements varies widely among individuals, and children may have severe alterations in some biochemical measures but not others [1]. Few studies have investigated empirical correlations among biochemical measures in children with DKA. Therefore, the extent to which theoretical physiological relationships hold true is unknown. Examining these correlations may provide insights into kidney function and acid–base physiology during DKA. We undertook the current study to investigate relationships between biochemical measures at DKA presentation in children.

Biochemical data from 1681 DKA episodes were included in these analyses. A total of 799 (47.5%) DKA episodes occurred in children with new onset of diabetes and the remaining 882 episodes in children with previously diagnosed diabetes. Mean age for the study sample was 11.1 (SD 4.2) years and 46.5% were male. Biochemical values at DKA presentation are summarized in Table 1. Blood pH and serum bicarbonate concentrations were among the most strongly correlated measures (r=0.64, Figure 1), however, pH and PCO_2 were only loosely correlated (r=0.17). The correlation between blood pH and serum glucose concentration was also modest (r=−0.19). Instead, glucose levels were more closely correlated with indicators of circulatory volume depletion and kidney function such as blood urea nitrogen (r=0.44), serum creatinine (r=0.42), and glucose-corrected serum sodium (r=0.32). Potassium levels at presentation were loosely correlated with pH (r=−0.21) as well as indicators of plasma tonicity (glucose corrected sodium: r=0.22, glucose: r=0.23). Potassium levels at presentation were more substantially correlated with measures of kidney function (BUN: r=0.38, creatinine: r=0.32). In a sensitivity analysis including only the first DKA episode for patients with two DKA episodes included in the database, correlations were nearly identical, and p-values remained <0.001 for all associations (data not shown).

Among children who had two DKA episodes during the study period (n=128), glucose, pH and bicarbonate levels during the two episodes were minimally correlated, however, PCO_2 levels at the first and second DKA episode were more strongly correlated (r=0.34; Figure 2). Measures related to kidney function and circulatory volume (glucose-corrected sodium, chloride, potassium, BUN, and creatinine levels) also tended to be similar between episodes in the same individual.

Table 1: Biochemical measures at DKA presentation (n=1,681 DKA episodes).

	Mean (SD)	Median (Q1–Q3)
Glucose, mg/dL	524 (175)	500 (410–600)
Glucose-corrected sodium, mEq/L	141.5 (5.7)	140.8 (137.7–144.6)
Potassium, mEq/L	4.9 (1.0)	4.8 (4.2–5.4)
Chloride, mEq/L	98.9 (6.2)	99.0 (95.0–103.0)
Bicarbonate, mEq/L	9.3 (3.6)	9.0 (6.0–12.0)
BUN, mg/dL	17.4 (8.3)	16.0 (12.0–21.0)
Creatinine z-score	0.7 (1.0)	0.5 (0.0–1.0)
PCO_2, mmHg	26.3 (7.5)	26.0 (21.0–31.0)
pH	7.17 (0.12)	7.19 (7.10–7.24)

Biochemical data from children with DKA at the time of presentation to the emergency department were obtained from the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies under Investigation in DKA (FLUID) Trial database. The PECARN FLUID Trial was a randomized, controlled trial evaluating the effects of intravenous fluid infusion rate and sodium content on neurocognitive outcomes of DKA in children (Kuppermann et al. NEJM, 2018; 378 (24): 2,275-87). The FLUID trial was conducted in 13 hospitals and involved 1,389 DKA episodes. To ensure that the current study database represented the full range of presentations of DKA in children, we augmented the FLUID Trial database by adding DKA episodes at PECARN hospitals during the trial dates in which patients were not included in the trial because of provider treatment preferences or severely altered mental status at presentation (n=379). As one site was unable to review the additional DKA records, we excluded all episodes enrolled at this site from the current analysis (12 PECARN FLUID study sites were included, n=1302 DKA episodes). The Institutional Review Boards at each of the participating institutions approved the study protocol as well as additional medical record review. We included children younger than 18 years with DKA defined by serum glucose >300 mg/dL and either venous pH<7.25 or serum bicarbonate concentration <15 mmol/L. Children who received substantial treatment for DKA before transfer to the PECARN study site were excluded. Children with more than one eligible DKA episode during the study period could be included at most twice. Glucose-corrected serum sodium concentrations were calculated according to the formula: corrected Na=measured Na + 1.6 ((blood glucose-100)/100). Creatinine values were age-adjusted using age-based reference values to calculate z-scores, where a z-score of 1 represents one standard deviation above the mean for age. Bicarbonate values were required to be from electrolyte panels, rather than blood gas analyses, to avoid using bicarbonate levels that are calculated rather than measured.

In summary, these analyses used a large database of DKA episodes in children to examine relationships among biochemical measures at DKA presentation. Notable findings included strong correlations between glucose levels and measures of kidney function/circulatory volume status, and lack of substantial correlations between pH and PCO_2 levels.

DKA involves multiple physiological perturbations including alterations related to acid-base balance, dehydration, hyperosmolality, electrolyte redistribution, and

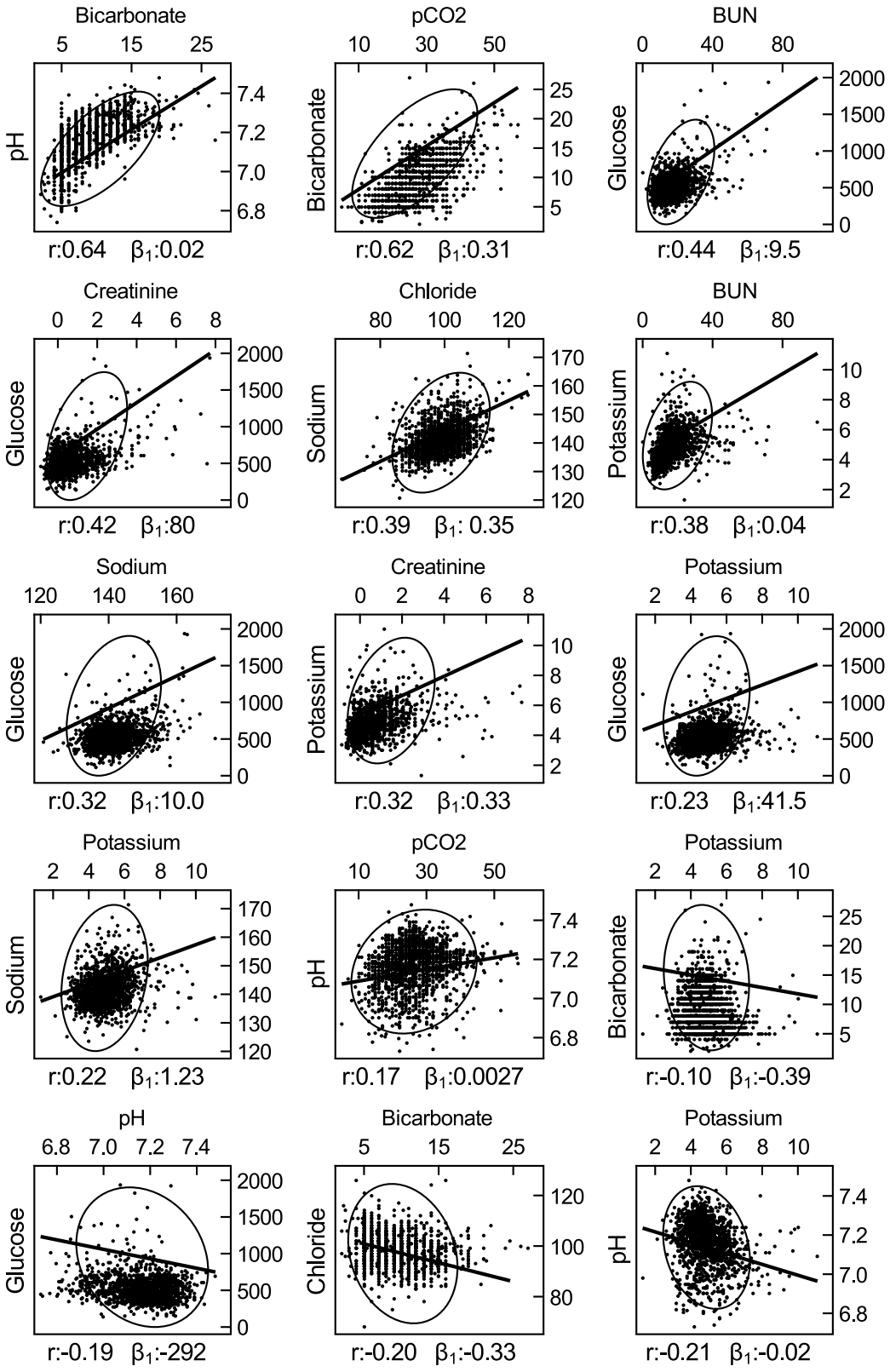

Figure 1: Correlations between biochemical measures in children with diabetic ketoacidosis, ordered by descending correlation estimates (p<0.001 for all correlations)*†‡. We computed Pearson correlation statistics to describe associations between baseline laboratory values recorded for each visit, and the probability of observing the same or higher correlation coefficient under the null hypothesis of zero correlation (p-value). We also calculated slope estimates to describe the relationship between laboratory measures using simple linear regression. To address possible effects related to multiple DKA

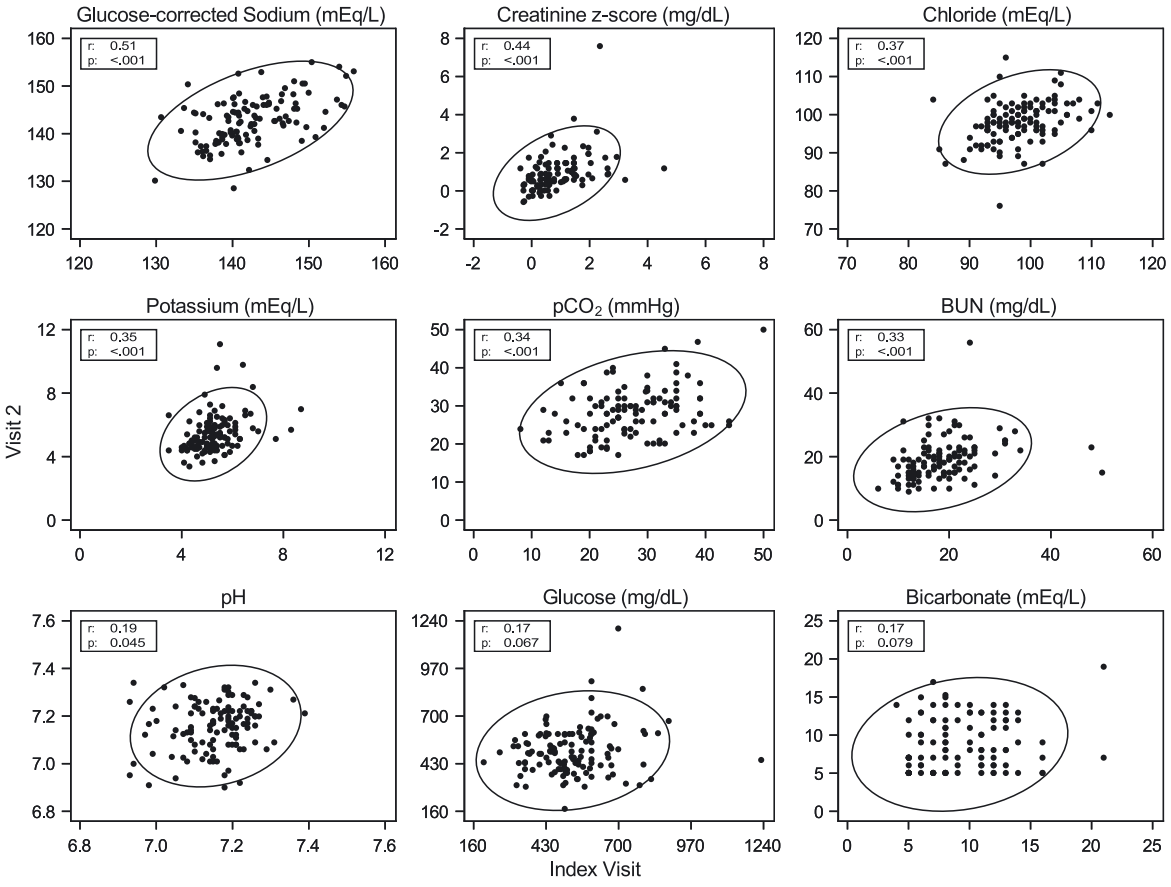

Figure 2: Correlations between biochemical measures among individuals presenting with two separate DKA episodes, ordered by descending correlation estimates. Among patients with two DKA episodes (n=128), we calculated Pearson correlations and p-values comparing baseline laboratory values at the first vs. second visit. *Graphs show 95% prediction elliptical curve. Note that some participants have either pH or bicarbonate levels above usual cutoffs for diagnosis of DKA because either pH<7.25 or serum bicarbonate concentration <15 mmol/L was used to define DKA. In addition, although the first measured biochemical values for study participants were recorded in the database, some patients had greater acidosis on subsequent measurements, meeting criteria for diagnosis of DKA sometime after the first biochemical measurements were made. †r: Pearson Correlation Coefficient; 95% prediction ellipses are shown which would be expected to contain 95% of new observations from the same population.

electrolyte loss. Observed biochemical alterations can be explained based on physiological principles, however, few studies have investigated whether relationships among measured biochemical values conform to expectations. Deviations from expected relationships among biochemical measures are informative and suggest that additional pathophysiological considerations must be explored.

In the 1970s, investigators proposed that markedly elevated glucose levels in patients with diabetes reflected reductions in glomerular filtration rate with reduced efficiency of glucose elimination [2]. Our analyses confirm these theoretical predictions, demonstrating that glucose concentrations are most closely correlated with measures of kidney function (BUN and creatinine concentrations) and

episodes in the same individuals, we re-calculated Pearson correlation statistics and p-values for baseline laboratory value associations after excluding repeat enrollments so that each patient was represented only once. Statistical analyses were performed using SAS/STAT software, version 9.4 (SAS Institute; Cary, NC). *Units are as follows: bicarbonate, chloride and potassium: mEq/L; PCO^2: mmHg; glucose, BUN: mg/dL; creatinine: *z*-score adjusted for age; sodium: mEq/L adjusted for glucose: measured sodium + 1.6 ([blood glucose-100]/100). †r: Pearson correlation coefficient. All p-values are <0.001; β^1: slope estimate from a linear regression model; 95% prediction ellipses are shown which would be expected to contain 95% of new observations from the same population. ‡ Some participants have either pH or bicarbonate levels above usual cutoffs for diagnosis of DKA because either pH<7.25 or serum bicarbonate concentration <15 mmol/L was used to define DKA. In addition, although the first measured biochemical values for study participants were recorded in the database, some patients had greater acidosis on subsequent measurements, meeting criteria for diagnosis of DKA sometime after the first biochemical measurements were made.

dehydration (glucose-corrected sodium concentrations). Also as expected, pH was strongly correlated with serum bicarbonate levels [3], and potassium levels were correlated with measures of kidney function, acidosis, and plasma tonicity [4–6]. Greater potassium efflux from cells is stimulated by increased plasma tonicity (causing water efflux from cells and creating a potassium gradient), low insulin levels, and buffering of hydrogen ions via potassium/hydrogen exchange [4–6]. Reductions in glomerular filtration rate also serve to limit urinary potassium excretion, maintaining higher serum potassium levels [5, 7].

Interestingly, we found that PCO_2 levels were only weakly correlated with pH values. Furthermore, children who experienced two episodes of DKA tended to have similar PCO_2 levels at each episode, although pH levels at the two episodes were only minimally correlated. A range of PCO_2 levels might be expected among children with DKA and near-normal pH values, however, substantial variability in PCO_2 levels among children with more severe acidosis suggests interference with respiratory compensation for metabolic acidosis [8]. Inappropriately elevated PCO_2 levels may be caused by respiratory fatigue [9] or may reflect abnormalities in cerebral perfusion affecting brainstem function [10]. Pulmonary edema has also been described in DKA [11], and may affect the efficiency of pulmonary gas exchange. In studies measuring end-tidal CO_2 in children with DKA, variation in the ventilatory response to acidosis was also observed among patients and was hypothesized to be caused by variation in the degree of CNS acidosis for any given blood pH value [12].

Children with repeated episodes of DKA also tended to have stereotyped alterations in kidney function and electrolyte balance. Previous studies have shown that acute kidney injury (AKI) occurs frequently in children with DKA and that occurrence of AKI during one DKA episode is strongly predictive of AKI at a subsequent DKA episode [13]. These findings suggest that physiological or genetic differences among individuals may influence kidney function during DKA.

The current study has some limitations. The first laboratory tests recorded at the participating institution were used for these analyses; however, in some cases, these may have been measured after receiving an initial intravenous fluid bolus. In addition, methods for measurement of serum creatinine concentrations varied among study sites. Marked elevation in acetoacetate is known to affect the accuracy of some creatinine assay methods [14]. This may have increased variability in creatinine measurements such that correlations between creatinine and other biochemical measures may in fact be somewhat stronger than those reported here.

In summary, these analyses provide insights into the physiological processes influencing biochemical alterations during DKA in children. In agreement with theoretical predictions, serum glucose levels at presentation were most strongly related to kidney function, with elevated glucose levels reflecting reductions in glomerular filtration rate. Potassium levels also followed predicted associations, varying according to acidosis, plasma tonicity, and kidney function. Interestingly, pH and PCO_2 were only weakly correlated, and PCO_2 levels tended to be similar in repeated episodes of DKA in the same individual. Our findings suggest that respiratory responses to acidosis during DKA vary among individuals and may be influenced by genetic factors, as well as pulmonary and central nervous system effects of DKA.

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Competing interests: None of the authors have conflicts of interest relevant to the manuscript.

Informed consent: Informed consent was obtained from all individuals included in the PECARN FLUID Trial database. Consent was not required for medical records review for the additional DKA episodes added later to the FLUID Trial database.

Ethical approval: The research related to human use has complied with all of the relevant national regulations, institutional policies, and in accordance with the tenets of the Helsinki Declaration. The Institutional Review Boards at each of the participating institutions approved the study protocol as well as additional medical record review.

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