Serum Sodium Concentration and Mental Status in Children With Diabetic Ketoacidosis

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abstract

OBJECTIVES: Diabetic ketoacidosis (DKA) is typically characterized by low or low-normal serum sodium concentrations, which rise as hyperglycemia resolves. In retrospective studies, researchers found associations between declines in sodium concentrations during DKA and cerebral injury. We prospectively investigated determinants of sodium concentration changes and associations with mental status alterations during DKA.

METHODS: Using data from the Pediatric Emergency Care Applied Research Network Fluid Therapies Under Investigation in Diabetic Ketoacidosis Trial, we compared children who had declines in glucose-corrected sodium concentrations with those who had rising or stable concentrations. Children were randomly assigned to 1 of 4 intravenous fluid protocols that differed in infusion rate and sodium content. Data from the first 4, 8, and 12 hours of treatment were analyzed for 1251, 1086, and 877 episodes, respectively.

RESULTS: In multivariable analyses, declines in glucose-corrected sodium concentrations were associated with higher sodium and chloride concentrations at presentation and with previously diagnosed diabetes. Treatment with 0.45% (vs 0.9%) sodium chloride fluids was also associated with declines in sodium concentration; however, higher rates of fluid infusion were associated with declines in sodium concentration only at 12 hours. Frequencies of abnormal Glasgow Coma Scale scores and clinical diagnoses of cerebral injury were similar in patients with and without declines in glucose-corrected sodium concentrations.

CONCLUSIONS: Changes in glucose-corrected sodium concentrations during DKA treatment are influenced by the balance of free-water loss versus sodium loss at presentation and the sodium content of intravenous fluids. Declines in glucose-corrected sodium concentrations are not associated with mental status changes during treatment.

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WHAT'S KNOWN ON THIS SUBJECT: Retrospective studies have shown associations between diabetic ketoacidosis (DKA)–related cerebral injury in children and declines in serum sodium concentrations. Factors influencing sodium concentration changes during DKA are poorly understood, and associations with cerebral injury have not been confirmed prospectively.

WHAT THIS STUDY ADDS: Serum sodium trends during DKA were mainly influenced by the balance of free-water versus sodium loss at presentation and intravenous fluid sodium content. Contrary to previous retrospective studies, declines in serum sodium concentrations were not associated with altered mental status.

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ARTICLE

Protocols for treatment of diabetic ketoacidosis (DKA) in children frequently recommend monitoring trends in serum sodium and glucose concentrations and modifying intravenous fluid treatment in response to these trends. These recommendations reflect concerns that rapid changes in osmolality might increase the risk of cerebral edema and cerebral injury. Retrospective studies found associations between declines in serum sodium concentrations during DKA treatment and increased risk of clinically apparent cerebral injury, lending support to these concerns.[1,2] Many current pediatric DKA guidelines therefore recommended using 0.9% sodium chloride (NaCl) solutions and conservative rates of fluid infusion.[3–6]

Recently, the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in Diabetic Ketoacidosis (FLUID) Trial prospectively assessed the impact of variations in intravenous fluid protocols on risk of mental status changes during treatment and on cognitive outcomes after recovery in children with DKA.[7] The PECARN FLUID Trial found no significant associations between either fluid infusion rate or sodium content and risk of acute or long-term neurologic injuries. In the current study, we analyzed clinical and biochemical data collected during the PECARN FLUID Trial to identify factors influencing changes in serum sodium concentrations during treatment and whether these changes are associated with mental status changes and risk of cerebral injury.

METHODS

Overview of PECARN FLUID Trial

In the current study, we analyzed data collected during the PECARN FLUID Trial.[7] Detailed methods[8] and results[7] from this trial were previously published. Relevant features of the trial are outlined here. The trial involved 13 PECARN-affiliated emergency departments located in urban centers in the United States. Trial participants were randomly assigned to 1 of 4 intravenous fluid protocols by using a 2 × 2 factorial study design. The protocols used either 0.45% or 0.9% NaCl solutions infused at either a more rapid or slower rate.[8] Children enrolled in the trial had ongoing monitoring of mental status during DKA treatment by using hourly Glasgow Coma Scale (GCS) score assessments and tests of short-term memory (digit span recall) every 4 hours during waking hours. Glucose levels were measured hourly, and electrolyte concentrations were measured every 2 to 4 hours.

Study Participants

Participants were 0 to 18 years old and were diagnosed with DKA (blood glucose level >300 mg/dL or 16.6 mmol/L, venous pH <7.25, or serum bicarbonate level <15 mmol/L and a urine or blood test positive for ketones). Children were excluded from the study for the following reasons: disorders that could alter cognitive function (alcohol or drug intoxication, head trauma, or neurologic diagnoses), substantial treatment of DKA before arrival at the study site, pregnancy, low GCS scores (≤11), or clinical scenarios for which treating physicians felt specific fluid and electrolyte therapy was required.

DKA Treatment Protocols

After obtaining written informed consent, children were randomly assigned to 1 of 4 treatment arms. Children in the slow infusion arms received an initial intravenous fluid bolus of 10 mL/kg of 0.9% NaCl solution. In the fast infusion arms, children received initial intravenous fluid boluses of 20 mL/kg of 0.9% NaCl solution. After the initial fluid bolus, in the slow infusion arms (one 0.45% NaCl arm and one 0.9% NaCl arm), infusion rates were calculated to replace an estimated fluid deficit of 5% of body weight evenly over 48 hours. In the fast infusion arms (one 0.45% NaCl and one 0.9% NaCl arm), infusion rates were calculated to replace an estimated fluid deficit of 10% of body weight, with half of the deficit replaced over the first 12 hours and the remaining half over the next 24 hours. Insulin treatment began after the intravenous fluid bolus as a continuous intravenous infusion of 0.1 U/kg per hour. Use of dextrose-containing fluids was initiated when the glucose concentration declined below 200 to 300 mg/dL (11.1–16.6 mmol/L). Potassium replacement was begun after the initial fluid bolus(es) by using an equal mixture of either potassium chloride and potassium phosphate or potassium acetate and potassium phosphate. Potassium replacement was identical among arms at each study site but varied among sites.

Biochemical and Neurocognitive Monitoring During DKA

Biochemical monitoring of patients followed international recommendations[9] and included hourly testing of glucose and measurement of electrolyte levels every 2 to 4 hours. The frequency of electrolyte testing within the 2- to 4-hour time window varied on the basis of provider discretion. All measured glucose and electrolyte values were recorded in the study database. Baseline laboratory values were defined as the first measured value before randomization.

GCS scores were recorded at enrollment and hourly thereafter. Abnormal GCS scores (<14) were rechecked after 15 minutes to confirm the abnormality. Diagnoses of clinically apparent cerebral injury

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(GCS score <14 associated with administration of either mannitol or hypertonic saline, intubation, or death) were also recorded. To address variations in diagnostic criteria for clinically apparent cerebral injury among clinicians, encounters involving hyperosmolar therapy, endotracheal intubation, or death were reviewed by an adjudication committee to confirm or reject the diagnosis of clinically apparent brain injury on the basis of published criteria.[10]

For children 3 years and older, tests of short-term memory (digit span recall) were conducted at enrollment and every 4 hours thereafter during normal waking hours.[8] In this test, participants are asked to repeat a sequence of numbers presented verbally, either in the order presented ("forward" task), or reverse order ("backward" task). The length of the digit span is increased by 1 in each successive round until the participant reports the sequence incorrectly in 2 spans of the same length. GCS score and digit span assessments continued for 24 hours or until DKA resolution (transition to subcutaneous insulin) if DKA resolved before 24 hours.

Outcome Measures and Comparisons

We calculated the glucose-corrected sodium concentration according to the following formula: corrected sodium concentration = measured sodium concentration + 1.6 ([blood glucose − 100]/100).[11] Glucose-corrected sodium concentration was calculated for values measured at baseline (before initiation of fluids) ± 1 hour and at 4 ± 1 hour, at 8 ± 1 hour, and at 12 ± 2 hours after initiation of study treatment. Episodes were excluded from the analysis of each 4-hour block if DKA resolved (transition to subcutaneous insulin) before 3, 7, and 10 hours, respectively. If DKA

had not resolved but a glucose-corrected sodium value was not available within a specific time window, we used multiple imputation to estimate these values (24% of values for 4-hour analyses, 27% for 8-hour analyses, and 12% for 12-hour analyses). We performed multiple imputation using sequential chained regression models.[12] Imputation models included demographic, clinical, biochemical (glucose and sodium values before and after the time window), treatment, and outcome information and used standard methods to combine results across imputations.[12]

Patients who had declines in glucose-corrected sodium concentrations between baseline and the 4-, 8-, or 12-hour time points were compared with those for whom the glucose-corrected sodium concentrations remained stable or increased to identify factors associated with a decline in glucose-corrected sodium concentration. In secondary analyses, we used glucose-corrected sodium concentration as a continuous variable to examine these associations. Mental status measures during treatment (GCS and digit span scores) were also compared between groups.

Statistical Analyses

We described categorical characteristics in the comparison groups using counts and proportions and tested for associations using likelihood ratio χ^2 tests. We described continuous characteristics using means and SDs and tested for associations using 2-sided Wilcoxon rank test with normal approximations and continuity corrections. We estimated unadjusted odds ratios for decline in glucose-corrected sodium concentration using logistic regression models for each of the

following: fast versus slow infusion rate, 0.45% vs 0.90% NaCl, baseline GCS score (<14 vs 14–15), age (years), previously diagnosed versus new-onset diabetes, dehydration (determined by change in body weight from presentation to discharge), and baseline laboratory values (serum urea nitrogen [SUN], creatinine, glucose-corrected sodium, chloride, and pH). We then fit a multivariable model using factors that had univariable P values <.20 and a fixed effect for study site. We used backward elimination variable selection by removing the factors with the largest type III P value ≥.05 one at a time, while retaining study site, fluid rate, and NaCl concentration assigned regardless of P value. Adjusted odds ratios for glucose-corrected sodium concentration decline versus stability or increase were estimated by using adjusted models for 4-, 8-, and 12-hour comparisons. In analyses evaluating glucose-corrected sodium concentration changes as a continuous outcome, we similarly applied linear regression methods to obtain unadjusted and adjusted regression coefficients associated with the same set of predictors.

We described mental status changes during DKA episodes in which glucose-corrected sodium concentrations declined and those in which glucose-corrected sodium concentrations remained stable or increased and tested for differences between these groups. Forward and backward digit span scores were compared by using linear regression models with a subject-level intercept and slope as well as fixed effects for site, age, sex, socioeconomic status (maternal education level), fluid rate and NaCl concentration, previous diabetes diagnosis, and baseline pH. We report cohort-specific slopes, which are average changes in digit span recall over time (points per

hour), along with SE and *P* values, used to test for group differences obtained from the regression models. Mental status changes (declines in GCS scores) and diagnoses of clinically apparent cerebral injury were compared between groups by using multivariable logistic regression models with adjustment for the same variables listed above. The model for clinically apparent cerebral injury was not adjusted for site because of the low number of outcomes.

To evaluate temporal associations between sodium concentration declines and altered mental status, we counted the number of DKA episodes in which a decline in glucose-corrected sodium concentration occurred during specific periods (before treatment initiation, 0–<4 hours, 4–<8 hours, 8–<12 hours, and >12 hours). During each period, we determined the number in which a decline in mental status (GCS score <14) occurred and compared those counts to the expected number, assuming no association between sodium concentration change and altered mental status. Finally, we used generalized estimating equations to fit a logistic regression model accounting for time and repeated measures to test for a temporal association between altered mental status and sodium concentration decline.

All analyses were performed by using SAS/STAT software (version 9.4; SAS Institute, Inc, Cary, NC). Multiple imputation was performed by using IVEware (version 0.3; University of Michigan, Ann Arbor, MI), and results from multiple imputations were combined by using the MIANALYZE procedure in SAS/STAT software.

RESULTS

Of the 1389 DKA episodes involved in the PECARN FLUID Trial, in 1251,

both glucose and sodium concentrations were recorded and intravenous insulin treatment of at least 3 hours was received after initiation of study fluid treatment (Fig 1); these episodes were therefore included in the 4-hour analysis. Intravenous insulin treatment was received for at least 7 hours after initiation of study fluid treatment in 1086 DKA episodes and for at least 10 hours in 877 episodes. These DKA episodes were included in the 8- and 12-hour analyses, respectively.

Patients who had declines in glucose-corrected sodium concentrations during treatment were older and more likely to have previously diagnosed diabetes. These patients also had higher initial glucose-corrected sodium, chloride, and creatinine concentrations and were more acidotic than patients for whom glucose-corrected sodium concentrations increased or remained stable. These associations

were consistent among the 4-, 8-, and 12-hour time points. Declines in glucose-corrected sodium concentrations were also more frequent in children assigned to the 0.45% NaCl treatment arms (Tables 1 through 4). More rapid fluid infusion was associated with declines in glucose-corrected sodium concentrations only at the 12-hour time point (Table 4).

In multivariable models, we determined which factors were associated with declines in glucose-corrected sodium concentrations after adjusting for the effects of other covariates (Tables 2 through 4). In these analyses, higher initial glucose-corrected sodium concentrations, higher initial chloride concentrations, previous diagnosis of diabetes, and assignment to the 0.45% NaCl treatment arms were significantly associated with declines in glucose-corrected sodium concentrations at all time points. More rapid fluid infusion was associated with
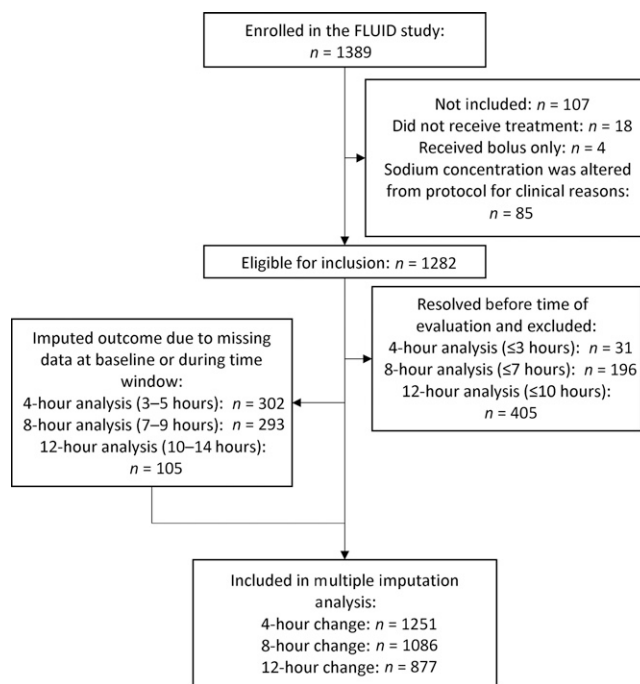

FIGURE 1
Participant flow diagram.

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TABLE 1 Characteristics of Participants According to 4-, 8-, and 12-Hour Changes in Glucose-Corrected Sodium Concentration

	4-h Glucose-Corrected Sodium Concentration			8-h Glucose-Corrected Sodium Concentration			12-h Glucose-Corrected Sodium Concentration		
	Glucose-Corrected Sodium Concentration Stable or Increased ($n = 521$)	Glucose-Corrected Sodium Concentration Decreased ($n = 730$)	P	Glucose-Corrected Sodium Concentration Stable or Increased ($n = 454$)	Glucose-Corrected Sodium Concentration Decreased ($n = 632$)	P	Glucose-Corrected Sodium Concentration Stable or Increased ($n = 377$)	Glucose-Corrected Sodium Concentration Decreased ($n = 500$)	P
Male sex	252 (48.3%)	337 (46.1%)	.48[a]	212 (46.7%)	291 (46.1%)	.70[a]	181 (48.0%)	233 (46.6%)	.70[a]
Age at screening, (years)	11.0 (4.4)	12.1 (3.7)	<.001[b]	10.9 (4.3)	12.0 (3.8)	<.001[b]	11.1 (4.3)	11.8 (4.0)	.01[b]
Race			.18[a]			.10[a]			.02[a]
Black	110 (21.1%)	149 (20.4%)		86 (19.0%)	142 (22.5%)		69 (18.3%)	117 (23.4%)	
White	356 (68.3%)	505 (69.2%)		327 (72.0%)	425 (67.3%)		274 (72.6%)	333 (66.6%)	
Other	21 (4.1%)	45 (6.1%)		15 (3.3%)	38 (6.0%)		11 (2.9%)	30 (6.0%)	
Unknown	35 (6.6%)	31 (4.2%)		26 (5.7%)	27 (4.3%)		23 (6.2%)	20 (4.0%)	
Ethnicity			.26[a]			.49[a]			.15[a]
Hispanic	89 (17.1%)	117 (16.0%)		75 (16.5%)	104 (16.5%)		60 (15.8%)	90 (18.1%)	
Not Hispanic	406 (78.0%)	591 (80.9%)		358 (78.9%)	508 (80.4%)		300 (79.7%)	399 (79.7%)	
Unknown	26 (4.9%)	22 (3.1%)		21 (4.6%)	20 (3.2%)		17 (4.5%)	11 (2.2%)	
Previously diagnosed with diabetes	214 (41.1%)	441 (60.4%)	<.001[a]	175 (38.6%)	366 (57.8%)	<.001[a]	148 (39.2%)	270 (54.0%)	<.001[a]
Assigned to fast treatment arm	267 (51.3%)	369 (50.5%)	.58[a]	224 (49.3%)	323 (51.2%)	.54[a]	175 (46.4%)	270 (54.0%)	.03[a]
Assigned to 0.90% NaCl treatment arm	337 (64.7%)	296 (40.5%)	<.001[a]	323 (71.1%)	235 (37.2%)	<.001[a]	275 (73.1%)	168 (33.5%)	<.001[a]
Baseline GCS score			.92[a]			.63[a]			.25[a]
<14	10 (1.8%)	12 (1.7%)		9 (2.0%)	13 (2.1%)		11 (3.0%)	7 (1.3%)	
14	36 (6.9%)	49 (6.7%)		30 (6.7%)	53 (8.3%)		30 (8.0%)	45 (9.0%)	
15	475 (91.2%)	669 (91.6%)		415 (91.3%)	566 (89.6%)		336 (89.0%)	449 (89.7%)	
Baseline SUN (mg/dL)	16.6 (7.6)	17.3 (7.1)	.02[b]	16.7 (7.8)	17.2 (7.3)	.09[b]	16.9 (7.9)	16.6 (7.2)	.89[b]
Baseline creatinine (mg/dL)	0.7 (0.36)	0.8 (0.33)	<.001[b]	0.7 (0.37)	0.8 (0.34)	<.001[b]	0.77 (0.40)	0.81 (0.34)	.001[b]
Baseline glucose-corrected sodium (mEq/L)	139.0 (4.7)	142.6 (4.8)	<.001[b]	138.6 (4.6)	143.0 (4.7)	<.001[b]	138.5 (4.9)	143.2 (4.7)	<.001[b]
Baseline chloride (mEq/L)	97.1 (6.5)	99.5 (5.4)	<.001[b]	97.1 (6.7)	99.6 (5.4)	<.001[b]	97.2 (6.9)	100.0 (5.4)	<.001[b]
Baseline glucose (mg/dL)	528 (160)	517 (144)	.23[b]	529 (167)	526 (141)	.59[b]	532 (177)	526 (137)	.44[b]
Baseline pH	7.17 (0.11)	7.15 (0.10)	.002[b]	7.17 (0.11)	7.14 (0.10)	<.001[b]	7.16 (0.11)	7.13 (0.10)	<.001[b]
Dehydration %	5.3 (5.0)	5.4 (4.3)	.51[b]	5.4 (4.5)	5.5 (4.7)	.58[b]	5.5 (4.7)	5.6 (4.7)	.48[b]

Data are presented as mean (SD) for continuous characteristics and n (%) for categorical characteristics. This table summarizes 10 multiply imputed data sets; numbers may not add up to the total because of rounding.

[a] Likelihood ratio χ^2 test.

[b] Two-sided Wilcoxon rank test with normal approximation and continuity correction.

TABLE 2 Unadjusted and Adjusted Odds Ratios of Glucose-Corrected Sodium Concentration Decreasing Versus Remaining Stable or Increasing Between Treatment Initiation and 4 Hours

Variable	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Assigned to the fast treatment arm	0.97 (0.74 to 1.26)	0.96 (0.70 to 1.32)
Assigned to 0.9% NaCl treatment arm	0.37 (0.28 to 0.49)	0.29 (0.21 to 0.40)
Baseline GCS score <14	0.92 (0.37 to 2.31)	—
Age	1.07 (1.04 to 1.10)	—
Previously diagnosed with diabetes	2.19 (1.68 to 2.86)	2.64 (1.89 to 3.68)
Baseline SUN (mg/dL)	1.01 (1.00 to 1.03)	—
Baseline creatinine (mg/dL)	1.80 (1.22 to 2.64)	—
Baseline glucose-corrected sodium (mEq/L)	1.19 (1.15 to 1.23)	1.16 (1.12 to 1.20)
Baseline chloride (mEq/L)	1.07 (1.05 to 1.10)	1.04 (1.01 to 1.07)
Glucose (mg/dL)[a]	0.95 (0.88 to 1.04)	—
pH[b]	0.83 (0.72 to 0.96)	—
Dehydration (% of discharge wt)	1.01 (0.97 to 1.04)	—

Multiple imputations were analyzed, and results were combined. $n = 1251$ DKA episodes. Odds ratios of >1 indicate greater odds of glucose-corrected sodium concentrations falling versus remaining stable or rising. The multivariable logistic regression model was obtained by backward variable selection. Clinical center was included in the multivariable model but is not shown. CI, confidence interval; —, variable not selected for inclusion in multivariable model (not significantly associated with outcome in multivariable model).

[a] Odds ratio per each 100-mg/dL increase in the baseline glucose concentration.
[b] Odds ratio per each 0.1 increase in pH.

declines in glucose-corrected sodium concentrations only at the 12-hour time point. In secondary analyses, we used multiple linear regression to identify factors associated with changes in glucose-corrected sodium concentration when this outcome was assessed as a continuous variable. These results were largely similar to those of the analyses evaluating trends in glucose-corrected sodium concentration as a dichotomous outcome (Supplemental Tables 7 through 9).

In additional analyses, we assessed associations between changes in glucose-corrected sodium concentrations and mental status during DKA treatment. There were no differences in the frequencies of decline in GCS scores below 14 during DKA treatment between patients who had a decrease in glucose-corrected sodium concentrations and those in whom the glucose-corrected sodium concentration increased or remained stable (Table 5). Rates of clinically diagnosed cerebral injury were also similar in the 2 groups, as were rates of improvement in short-term memory function (digit span recall scores) during DKA treatment. To further assess temporal associations between declines in glucose-corrected sodium levels and mental status changes, we tabulated the observed number of episodes with declines in mental status, declines in glucose-corrected sodium concentrations, both, or neither during each 4-hour block. We calculated expected counts of DKA episodes in each category under the assumption of no association between sodium change and altered mental status and compared expected to observed counts. Observed counts were similar to expected counts, and a repeated-measure analysis revealed no significant association between sodium change and altered mental status over time ($P = .29$; Table 6).

DISCUSSION

Ideal management of sodium and fluid balance during DKA treatment in children has been a subject of controversy.[6,13–15] Pediatric DKA protocols frequently recommend monitoring trends in sodium concentrations and adjusting intravenous fluids to maintain an upward trend in the measured serum sodium concentration as the blood glucose level decreases, thereby preventing declines in the glucose-corrected sodium concentration and associated reductions in osmolality. Data from the current study provide helpful information to guide clinical decision-making regarding management of serum sodium trends during DKA treatment. First, sodium trends during treatment

TABLE 3 Unadjusted and Adjusted Odds Ratios of Glucose-Corrected Sodium Concentration Declining Versus Remaining Stable or Increasing Between Treatment Initiation and 8 Hours

Variable	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Assigned to the fast treatment arm	1.08 (0.83 to 1.41)	1.05 (0.75 to 1.49)
Assigned to 0.9% NaCl treatment arm	0.24 (0.18 to 0.33)	0.14 (0.09 to 0.21)
Baseline GCS score <14	1.04 (0.42 to 2.58)	—
Age	1.06 (1.03 to 1.10)	—
Previously diagnosed with diabetes	2.18 (1.67 to 2.85)	3.06 (2.14 to 4.38)
Baseline SUN (mg/dL)	1.01 (0.99 to 1.03)	—
Baseline creatinine (mg/dL)	2.02 (1.26 to 3.24)	—
Baseline glucose-corrected sodium (mEq/L)	1.26 (1.21 to 1.30)	1.26 (1.20 to 1.31)
Baseline chloride (mEq/L)	1.07 (1.05 to 1.09)	1.04 (1.00 to 1.07)
Baseline glucose (mg/dL)[a]	0.99 (0.91 to 1.08)	—
pH[b]	0.77 (0.67 to 0.88)	—
Dehydration (% of discharge wt)	1.00 (0.97 to 1.04)	—

Multiple imputations were analyzed, and results were combined. $n = 1086$ DKA episodes. Odds ratios of >1 indicate greater odds of glucose-corrected sodium concentrations falling versus remaining stable or rising. The multivariable logistic regression model was obtained by backward variable selection. Clinical center was included in the multivariable model but is not shown. CI, confidence interval; —, variable not selected for inclusion in multivariable model (not significantly associated with outcome in multivariable model).

[a] Odds ratio per each 100-mg/dL increase in the baseline glucose concentration.
[b] Odds ratio per each 0.1 increase in pH.

TABLE 4 Unadjusted and Adjusted Odds Ratios of Glucose-Corrected Sodium Concentration Declining Versus Remaining Stable or Increasing Between Treatment Initiation and 12 Hours

Variable	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Assigned to the fast treatment arm	1.36 (1.03 to 1.79)	1.56 (1.07 to 2.27)
Assigned to 0.9% NaCl treatment arm	0.19 (0.14 to 0.25)	0.08 (0.05 to 0.12)
Baseline GCS score <14	0.44 (0.15 to 1.26)	—
Age	1.04 (1.01 to 1.08)	—
Previously diagnosed with diabetes	1.82 (1.37 to 2.42)	3.27 (2.15 to 4.98)
Baseline SUN (mg/dL)	0.99 (0.98 to 1.01)	—
Baseline creatinine (mg/dL)	1.37 (0.93 to 2.02)	—
Baseline glucose-corrected sodium (mEq/L)	1.26 (1.20 to 1.31)	1.27 (1.19 to 1.34)
Baseline chloride (mEq/L)	1.08 (1.06 to 1.11)	1.09 (1.04 to 1.13)
Baseline glucose (mg/dL)[a]	0.98 (0.89 to 1.07)	—
pH[b]	0.78 (0.67 to 0.90)	—
Dehydration (% of discharge wt)	1.00 (0.97 to 1.04)	—

Multiple imputations were analyzed, and results were combined. $n = 877$ DKA episodes. Odds ratios of >1 indicate greater odds of glucose-corrected sodium concentrations falling versus remaining stable or rising. The multivariable logistic regression model was obtained by backward variable selection. Clinical center was included in the multivariable model but is not shown. CI, confidence interval; —, variable not selected for inclusion in multivariable model (not significantly associated with outcome in multivariable model).

[a] Odds ratio per each 100-mg/dL increase in the baseline glucose concentration.
[b] Odds ratio per each 0.1 increase in pH.

largely reflected the balance of sodium and water losses at presentation. As expected, patients who presented with higher initial sodium concentrations (indicating greater free-water losses) appropriately normalized sodium concentrations during treatment. Furthermore, the sodium content of intravenous fluids significantly influenced changes in sodium concentrations during treatment, but the rate of infusion of intravenous fluids had minimal effects. Finally, declines in glucose-corrected sodium concentrations were not associated with altered mental status during DKA treatment or clinically apparent cerebral injury.

In the PECARN FLUID Trial, we found that neither the rate of fluid infusion nor the sodium content of infused fluids was associated with risk of adverse neurologic outcomes of DKA treatment.[7] Previous retrospective studies, however, have revealed associations between declines in serum sodium concentrations during DKA treatment and risk of cerebral injury.[1,2] The current analyses therefore provide important data to address concerns about risk of cerebral injury in patient subgroups defined by serum sodium trends. Interestingly, rates of adverse neurologic events and measures of mental status during DKA were not significantly different between DKA episodes in which there was a decline in glucose-corrected sodium concentration and those in which the sodium concentration remained stable or increased. These findings are notable and likely reflect differences in study methods between the current prospective study and previous studies in which data were abstracted from medical records retrospectively. In retrospective studies, patient monitoring was not standardized, and episodes of cerebral injury were likely detected later in the course of illness. Adverse outcomes of cerebral injury in previous retrospective studies were also more common than in the PECARN FLUID Trial, suggesting more severe disease or delayed detection of cerebral injury in the absence of standardized monitoring of mental status.[1,2,16] Serum sodium measurements at the time of

diagnosis of cerebral injury in patients with injuries detected later in the course of disease might have reflected abnormalities in sodium homeostasis that resulted from cerebral dysfunction rather than the effects of fluid treatment protocols. Aberrations in secretion of antidiuretic hormone (syndrome of inappropriate antidiuretic hormone secretion) and natriuretic peptides (cerebral salt-wasting syndrome) may occur in patients with brain injuries because of diverse etiologies.[17] It is possible that secretion of either or both of these hormones may be affected in patients with advanced DKA-related brain injury.

Interestingly, patients with previously diagnosed diabetes were more likely to have declines in glucose-corrected sodium concentrations during treatment, even after adjustment for initial laboratory values and other covariates. The reason for this association is unclear but may reflect differences in renal sodium retention (increased proximal tubular sodium reabsorption) in patients with newly or recently diagnosed diabetes compared with those with a longer duration of diabetes.[18–20]

The current study has some limitations that should be kept in mind when interpreting the data. First, the PECARN FLUID Trial investigated variations in intravenous fluid protocols within the range of protocols typically used in the United States. We have not investigated whether fluid treatment outside of this range might cause greater alterations in serum sodium concentrations or whether these alterations could be associated with mental status changes. In addition, clinical indicators of possible cerebral dysfunction other than GCS scores (eg, alterations in vital signs) were not used to define neurologic

TABLE 5 Association Between Changes in Glucose-Corrected Sodium Concentration and Mental Status

	Glucose-Corrected Sodium Concentration Stable or Increased	Glucose-Corrected Sodium Concentration Decreased	Unadjusted P	Adjusted P
4-h outcomes				
Presented with GCS score ≥14, n	511	718		
GCS score declined below 14, n (%)[a]	17 (3.2)	21 (2.9)	.73	.73
All visits, n	521	730		
Clinically apparent cerebral injury, n (%)[a]	3 (0.6)	3 (0.4)	.68	>.99
Forward digit span, slope (SE)[b]	0.05 (0.01)	0.06 (0.01)	.33	.33
Backward digit span, slope (SE)[b]	0.04 (0.01)	0.06 (0.01)	.36	.24
8-h outcomes				
Presented with GCS score ≥14, n	445	619		
GCS score declined below 14, n (%)[a]	17 (3.9)	20 (3.2)	.60	.92
All visits, n	454	632		
Clinically apparent cerebral injury, n (%)[a]	4 (0.9)	2 (0.3)	.24	.27
Forward digit span, slope (SE)[b]	0.05 (0.01)	0.06 (0.01)	.33	.25
Backward digit span, slope (SE)[b]	0.04 (0.01)	0.06 (0.01)	.26	.16
12-h outcomes				
Presented with GCS score ≥14, n	366	493		
GCS score declined below 14, n (%)[a]	18 (4.9)	16 (3.3)	.24	.33
All visits, n	377	500		
Clinically apparent cerebral injury, n (%)[a]	4 (1.1)	2 (0.4)	.26	.26
Forward digit span, slope (SE)[b]	0.05 (0.01)	0.06 (0.01)	.67	.26
Backward digit span, slope (SE)[b]	0.04 (0.01)	0.06 (0.01)	.36	.16

All models excluded visits that resolved before the outcome of interest and combined results from 10 imputed data sets to account for missing covariate values.

[a] P value from logistic regression; the adjusted P value adjusts for sex, socioeconomic status, treatment group, previous diagnosis, baseline pH, age, and site (GCS model only).

[b] P value from mixed-effect linear regression with a subject-level intercept and slope; the adjusted P value adjusts for site, sex, socioeconomic status, treatment group, previous diagnosis, baseline pH, and age.

events, and so some indicators of neurologic dysfunction might have been missed. However, vital sign changes and other clinical indicators typically occur with more advanced cerebral dysfunction that would also include alternations in GCS scores. Furthermore, tests of short-term memory (hippocampal function) were the only measures of subtle neurologic dysfunction included in the study. Because DKA might not affect all brain regions equally, we cannot exclude the possibility that regions involved in functions other than memory might have been affected. Previous animal studies have revealed, however, that the hippocampus tends to be the brain region primarily affected in DKA-related brain injury.[21,22]

CONCLUSIONS

Our analyses of data from a large prospectively enrolled group of children with DKA reveal that changes in glucose-corrected sodium concentrations during treatment are mainly influenced by the initial sodium values at presentation and the sodium content of infused fluids. The rate of fluid infusion plays a minimal role. Furthermore, in contrast to data from previous retrospective studies, the risk of cerebral injury was not increased in DKA episodes in which glucose-corrected sodium

TABLE 6 Associations Between Changes in Glucose-Corrected Sodium Concentrations and Altered Mental Status During DKA Treatment: Actual Versus Expected Number of Patients per Group Under an Assumption of Independence Between GCS Score Decline and Sodium Concentration Decline

Time Period	Normal GCS Score and Stable or Increasing Sodium Concentration, Actual/Expected No.	Decline in GCS Score and Stable or Increasing Sodium Concentration, Actual/Expected No.	Normal GCS Score and Decline in Sodium Concentration, Actual/Expected No.	Decline in GCS Score and Decline in Sodium Concentration, Actual/Expected No.
Before fluid initiation	1252/1252.4	4/3.6	133/132.6	0/0.4
0–<4 h	817/818.6	29/27.4	527/525.4	16/17.6
4–<8 h	581/581.5	16/15.5	772/771.5	20/20.5
8–<12 h	708/709.1	12/10.9	660/658.9	9/10.1
≥12 h	689/687.0	4/6.0	688/690.0	8/6.0

Using a generalized estimating equation logistic regression model accounting for time and repeated measures, we found no association between decline in glucose-corrected sodium concentration and decline in GCS score during DKA treatment ($P = .29$).

concentrations declined during treatment.

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ABBREVIATIONS

DKA: diabetic ketoacidosis
FLUID: Fluid Therapies Under Investigation in Diabetic Ketoacidosis
GCS: Glasgow Coma Scale
NaCl: sodium chloride
PECARN: Pediatric Emergency Care Applied Research Network
SUN: serum urea nitrogen

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