CME

Diabetic Ketoalkalosis in Children and Adults

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Objectives: Diabetic ketoacidosis (DKA) with metabolic alkalosis (diabetic ketoalkalosis [DKALK]) in adults has been described in the literature, but not in the pediatric population. The discordance in the change in the anion gap (AG) and the bicarbonate is depicted by an elevated delta ratio (DR; rise in AG/drop in bicarbonate), which is normally approximately 1. The primary aim of this study was to determine whether DKALK occurs in the pediatric population, as has been seen previously in the adult population. The secondary aim was to determine the factors that may be associated with DKALK.

Methods: A retrospective analysis of adult and pediatric cases with a primary or secondary discharge diagnosis of DKA between May 2008 and August 2010 at a large urban hospital was performed. DKALK was assumed to be present if the DR was >1.2 or in cases of elevated bicarbonate.

Results: Of 190 DKA cases, 91 were children, with 21% fulfilling the criterion for DKALK. There were 99 adult cases, 35% of which fulfilled the criterion for DKALK. Our final logistic model revealed that among patients with a discharge diagnosis of DKA, male patients, patients with a history of renal failure, and patients presenting with abdominal findings on physical examination were at greater odds of having a concomitant metabolic alkalosis.

Conclusions: Although DKALK has been described in adults, it can occur in a significant number of children presenting with DKA. The recognition of DKA can be obscured in such situations unless the AG and DR are calculated because the pH and bicarbonate may be near normal or even elevated. In addition to having interesting biochemical features as a complex acid-base disorder, DKALK can pose diagnostic and/or therapeutic challenges.

Key Words: delta ratio, diabetic ketoacidosis, diabetic ketoalkalosis, metabolic alkalosis

Diabetic ketoacidosis (DKA), a common and serious disorder that almost always results in hospitalization, is defined by the presence of hyperglycemia, reduced pH, metabolic acidosis, elevated anion gap (AG), and serum or urine ketones.[1] In some situations, a metabolic alkalosis coexists with DKA and may normalize the pH and serum bicarbonate; therefore, the usual definition of DKA is not met. Bleicher coined the term diabetic ketoalkalosis (DKALK) for this entity in 1967,[2] although DKA with metabolic alkalosis had been described first in 1959.[3] Since Bleicher's description, more than 30 cases have been published in the English-language literature.

Although criteria for the presence of DKALK have been insufficiently studied and are not generally established, the use of the delta ratio (DR) is favored.[4] DR denotes the rise in the AG, divided by the drop in serum bicarbonate, when this value is below the normal range. The serum bicarbonate may be higher than the normal value in some cases, assuming that serum bicarbonate did indeed decrease by the same number that the AG increased but started at a higher level.[5] In such cases, when an AG is present, in the appropriate clinical setting a metabolic alkalosis and DKA are present; however, DR cannot be calculated—instead, an excess AG is present. Some authors have objected to the term DKALK because the metabolic alkalosis is not directly

Key Points

- Diabetic ketoalkalosis (DKALK) is seen with diabetic ketoacidosis and a concomitant metabolic alkalosis.
- DKALK may be recognized by calculating the delta ratio, which may illustrate the possible discordance between the change in anion gap and the change in bicarbonate, in combination with considering additional information from a medical history and physical examination.
- Recognition of DKALK may prevent diabetic ketoacidosis cases from being unrecognized.
- DKALK is seen in both pediatric and adult patients.

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The study was funded by a Summer Research Internship grant (E.A.H.) and the Department of Medicine, University of South Carolina School of Medicine, Columbia.

The authors have no financial relationships to disclose and no conflicts of interest to report.

Accepted July 10, 2013.

0038-4348/0–2000/107-6
DOI: 10.1097/SMJ.0000000000000040

Table 1. Candidate predictor variables

Demographics
Age (dichotomized at younger than 18 years)
Sex
Race
Medicaid insurance
Admission information
Primary diagnosis of diabetic ketoacidosis
Type 1 diabetes mellitus
Diagnosis of acute or chronic renal failure[a]
Diagnosis of cellulitis
Diagnosis of urinary tract infection
Diagnosis of pneumonia
First admission of diabetic ketoacidosis
Diagnosis of dehydration
Diagnosis of history of noncompliance
Diagnosis of streptococcal pharyngitis
Diagnosis of gastroparesis
Admission vitals
Temperature
Systolic blood pressure
Body mass index
Pulse
Diastolic blood pressure
Admission symptoms
Nausea and vomiting
Abdominal pain
Excessive thirst or polydipsia
Change in mental status
Change in weight
Objective signs on physical examination
Dehydration
Abdominal
Neurologic
Infection
Chest
Admission laboratory values
Arterial pH
pO_2
Potassium
Creatinine
Urine specific gravity
Hemoglobin
Hemoglobin A1c
pCO_2
Percent O_2 saturation
Blood urea nitrogen
Glucose
White blood cell count
Platelet count
Urine ketones
Admission studies
Abdominal films ordered
Precipitating cause
New diagnosis of diabetes mellitus
Noncompliance
Infection
Diet
Other

[a]*Screened in simple logistical regression as acute renal failure, chronic renal failure, and renal failure (acute or chronic).*

linked to the ketosis[6]; rather, it may be related to the volume depletion seen in DKA.

There was no large, systematic study of this entity until our brief report in adults.[7] A review of the pediatrics literature and textbooks does not describe this association of two primary acid-base disorders in children, nor was it familiar to our pediatrics colleagues. It is unclear whether this is a failure to recognize or to report the metabolic alkalosis and DKA in children. Although there is a report of ketoalkalosis occurring in a 9-year-old, this was a central respiratory alkalosis related to Rett syndrome that persisted after correction of the DKA.[8]

The primary aim of this study was to determine whether DKALK occurs in the pediatric population, as has been seen previously in the adult population. The secondary aim was to determine the factors that may be associated with DKALK. We report the findings of a retrospective chart review conducted using a liberal definition of DKALK.

Methods

Study Design

A retrospective review of records for all pediatric and adult patients with a primary or secondary diagnosis of DKA admitted between May 2008 and August 2010 was performed at a 650-bed teaching hospital. The institutional review board granted study approval based upon its exempt status. The hospital informatics department mined 213 cases and provided these to the study team. A total of 23 cases were excluded from data collection secondary to incomplete or absent serum sodium, chloride, and bicarbonate. Information from the remaining 190 cases was deidentified and data acquisition sheets were completed for each case.

Statistical Analysis

DKALK was defined as having a DR >1.2 or a serum bicarbonate ≥24 mEq/dL. AG was calculated using the conventional formula of $[Na - (Cl + HCO^{3-})]$. DR was calculated based upon the following formula [(calculated AG – 12)/(24 – serum bicarbonate)], with 12 and 24 accepted as the normal value for AG and serum bicarbonate, respectively.

Table 2. Final regression model with DKALK as outcome

	OR[a]	95% CI	*P*
Sex	2.92	1.40–6.10	0.004
Renal failure	5.14	2.18–2.13	<0.001
Abdominal findings	2.90	1.27–6.60	0.011

[a]*Odds of a patient with discharge diagnosis of DKA having superimposed metabolic alkalosis is 2.92 times greater for male patients than for female patients, after adjusting for other two factors.*
CI, confidence interval; DKA, diabetic ketoacidosis; DKALK, diabetic ketoalkalosis; OR, odds ratio.

Seventy-two potential predictor variables (demographic, clinical, and laboratory data) were initially collected. Of these, 17 were rejected because of missing values across the sample, leaving 55 potential predictors. Serum sodium, chloride, and bicarbonate were excluded as candidate predictor variables secondary to their use in the calculation of the outcome variable, DR, allowing investigation into the role of other variables. The deidentified data were transferred to an electronic data sheet to perform analysis.

The 52 potential predictor variables (Table 1) were screened with simple logistic regression, using DKALK as the outcome and a *P* value of 0.25 as the criterion. The full model obtained through this process then underwent a logistic regression model building process (R version 2.11.0, R Foundation for Statistical Computing) using the likelihood ratio test.

Results

When the 52 candidate predictor variables remaining were screened with simple logistic regression, a full logistic model was developed and consisted of the following predictors with DKALK as the outcome: age (dichotomized at younger than 18 years), sex, race (dichotomized as black or nonblack), history of acute or chronic renal failure, change in mental status, objective abdominal findings on examination, presence of nausea and vomiting, subjective thirst or polydipsia, and blood glucose level. By using the likelihood ratio test with $\alpha = 0.05$, age, race, change in mental status, nausea and vomiting, subjective thirst or polydipsia, and blood glucose level were dropped from the model. The final model, including odds ratios with 95% confidence limits and *P* values, is displayed in Table 2.

There were 190 cases with a primary or secondary discharge diagnosis of DKA. Ninety-one of the 190 were pediatric cases (patients younger than 18 years) with a mean age of 12 years; 89 (97.8%) had type 1 diabetes mellitus and 19 (21%) fulfilled the criteria for DKALK with a DR >1.2 or serum bicarbonate ≥ 24. There were 99 cases in the adult group with a mean age of 38 years; 67 (68%) had type 1 diabetes mellitus and 35 (35%) had features of DKALK. Table 3 contains additional demographic findings.

Our final logistic regression model with DKALK as the outcome used the categorical variables of sex, presence of acute or chronic renal failure, and objective abdominal findings on examination. The odds of a patient who was discharged from the hospital with a diagnosis of DKA having a superimposed alkalosis (DKALK) is 2.92 (95% confidence interval [CI] 1.40–6.10) times greater for male patients than female patients, after adjusting for whether the patient had a diagnosis of acute or chronic renal failure and adjusting for whether there were objective abdominal findings on examination. Similarly, the odds were 5.14 times greater (95% CI 2.18–12.13) among those with a diagnosis of renal failure than among those who did not, after adjusting for sex and objective abdominal findings. The odds were 2.90 times higher (95% CI 1.27–6.60) for those with objective abdominal findings than those without such findings, after adjusting for sex and whether there was a diagnosis of renal failure.

Discussion

The impetus for this study stemmed from the surprising frequency with which we saw cases of DKALK on the adult

Table 3. Comparison of pediatric and adult patients

		Pediatric		Adult		
	All, n = 190	DKA, n = 72	DKALK, n = 19	DKA, n = 64	DKALK (n = 35)	*P*[b]
Age	25.4	11.9	13.6	37.0	38.7	NA
Arterial pH	7.18	7.14	7.19	7.19	7.21	0.702
HCO^{3-}	10.5	8.7	13.1	10.1	13.6	0.862
AG	25.6	24.8	27.4	23.8	29.3	0.446
Length of stay, d	5.3	4.1	3.9	5.9	7.6	0.004
T1DM[a]	82%	97%	100%	69%	66%	0.011
Vomiting[a]	77%	83%	79%	72%	71%	0.782

[a]*Values in first five columns are mean, except these two categorical variables.*
[b]*P values are for the comparison of pediatric and adult patients with DKALK. The Mann-Whitney U test was used for continuous variable and the Fisher exact test was used for the two categorical variables.*
AG, anion gap; DKA, diabetic ketoacidosis; DKALK, diabetic ketoalkalosis; T1DM, type 1 diabetes mellitus.

inpatient teaching services that seemed obvious once the disorder was appreciated. We also wondered whether DKALK occurred in children, as had been seen in the adult population. The diagnosis of DKA is usually straightforward; in an appropriate clinical setting, its features include hyperglycemia, elevated AG, presence of ketones, and an appropriately reduced bicarbonate.[1] Many factors, however, may alter the acid-base milieu in the disorder, and a concomitant primary metabolic alkalosis may be overlooked if the values are not strikingly unusual. If the pH and bicarbonate are near normal and the AG is not calculated, then the alkalosis may go unnoticed and DKA may be missed. Fortunately, the treatments for the volume depletion, insulin deficiency, hyperglycemia, and electrolyte abnormalities usually address all of the irregularities that occur. As such, the question of whether the general definition of DKA should be modified to account for the presence of a concomitant or occult metabolic alkalosis/DKALK is debatable.

In simple AG metabolic acidosis of DKA, the AG should rise as much as the bicarbonate value decreases; in other words, DR = rise of AG/drop of bicarbonate = 1.[9] Thus, there is usually a 1:1 relation between the delta gap and the excess AG.[9] When the DR is >1.2, a metabolic alkalosis may be present; conversely, when the DR is <0.8, a non-AG metabolic acidosis may exist.[4] In accordance with previously used criteria, the current analysis relied on a DR >1.2 in the setting of DKA to identify a concomitant metabolic alkalosis. Using data from Androgue et al,[11] the mean bicarbonate deficit in plasma is approximately equal to the excess AG in patients admitted with diabetic ketoacidosis.[4,10–12] Some studies suggest that the use of DR >1.2 may result in overdiagnosis of mixed acid-base disorders and therefore emphasize the importance of considering additional information such as history, physical examination, and arterial blood gas measurement.[4,13] There is no other standardized formula to apply to the population.

We reviewed 36 of the previous published DKALK cases published in English by searching PubMed for multiple related terms and the bibliographies of the reports.[2,3,12,14–35] Many cases had a strikingly elevated bicarbonate and pH along with hyperglycemia and high AGs, which must have initiated closer inspection of these cases. All of the reported cases were in adults and exhibited ketonuria or ketonemia. The reports date to 1959 and include a review by Elisaf et al of 40 cases of DKA, 9 of which had DKA with coexisting metabolic alkalosis.[12] An analysis of these cases found a mean pH of 7.55 (7.30–7.70) and a mean AG of 25 (14–44). The DRs for all 36 cases were elevated or could not be calculated because the bicarbonate was above the normal value. All such cases were alkalemic; thus DR was not required to identify the disorder.[35] Almost all of the reports of DKALK have had either vomiting[3,12,14,15,18,20–23,25,26,28,30–32,34] as a prominent feature or another factor that may have caused metabolic alkalosis such as diuretic use[15,16,24,27,29,35] or corticosteroid excess.[3,19,20,27,29,35]

Most of the reports we studied posit volume depletion as the cause of the metabolic alkalosis in DKALK. One postulated mechanism may be that vomiting, osmotic diuresis, and reduced fluid intake contribute to volume depletion and a state of secondary hyperaldosteronism, potassium depletion, and hypochloremia, thus promoting renal bicarbonate conservation.[22] Elisaf et al indicated that patients with coexisting metabolic alkalosis had the most severe degree of hypovolemia, with lower serum levels of potassium, sodium, and chloride compared with other patients with DKA.[12]

For the present analysis, we collected multiple variables that may indicate volume depletion, including subjective thirst or polydipsia, nausea and vomiting, and examination findings that are consistent with dehydration. None of these variables were found to be associated with superimposed metabolic alkalosis in patients with a discharge diagnosis of DKA. Much of the literature we reviewed mentioned abdominal findings (subjective and/or objective) in presentation.[2,10,14,19,21–23,28] As discussed earlier, we did discover that patients with a discharge diagnosis of DKA who presented with objective abdominal findings on physical examination were at greater odds for meeting criteria for DKALK than patients without objective abdominal findings. It may be that the presence of abdominal findings on physical examination in patients with DKA indicates a more severe complex acid-base disturbance.

Our final model showed that in patients with the categorical variable of renal failure (acute and chronic), the odds for superimposed DKALK were 5.14 times greater ($P < 0.001$) than in patients with DKALK alone. The physiological events occurring in the renal system alter the relation between bicarbonate deficit and excess AG in DKA.[11] Patients with DKA who develop significant volume depletion, commonly as a result of osmotic diuresis or vomiting, will present with the classic AG type of metabolic acidosis secondary to reduced excretion of ketone salt, whereas patients with renal insufficiency also will retain these bicarbonate precursors.[4,36]

We previously reported a series of 156 DKA cases and 18 DKALK cases (11.5%) in adults with an association of older age and the presence of vomiting.[6] The prevalence of DKALK in adults in the present report was 35% in comparison to the prior 11.5%. Both studies used a DR >1.2 as a criterion for DKALK and assumed that both populations were similar. Another report found a 23% prevalence of DKALK in adults.[12] As such, a relatively wide range of prevalence is seen; regardless, the prevalence does appear to be noteworthy.

This analysis shows that DKA with superimposed metabolic alkalosis does in fact occur in both the pediatric and adult populations. It remains perplexing that DKALK in children has not been noted previously. Although there appears to be little harm from failure to recognize the metabolic alkalosis if DKA is diagnosed and treated appropriately, the recognition of DKA can be obscured unless the AG, DR, and ketones are appreciated because the pH and bicarbonate may be near normal or even elevated. Although DKA is straightforward to diagnose with rapid availability of electrolytes, pH, glucose, and ketone tests, it remains essential to calculate the AG and DR as well as

Table 4. Proposed DKA-DKALK criteria

	Accepted criteria[1]	Proposed criteria[a]
Plasma glucose	>250 mg/dL	>250 mg/dL
Arterial pH	<7.30	Variable
Serum bicarbonate	<18 mEq/dL	Variable
Urine ketone	Positive	Positive
Serum ketone	Positive	Positive
Anion gap	>10	>12
Effective serum osmolality	Variable	Variable

[a]*With consideration of delta ratio to aid in the diagnosis of cases of DKA, with superimposed metabolic alkalosis.*
DKA, diabetic ketoacidosis; DKALK, diabetic ketoalkalosis.

have an awareness of the full clinical picture. In the proper clinical scenario, our proposed revision of the diagnostic criteria for DKA would help to identify cases of DKA that do not meet the standard definition of the disorder (Table 4).

There are several limitations to this study. First, the retrospective nature of the study and use of the discharge diagnosis of DKA limit full evaluation of DKALK cases, because they may remain unidentified without proper recognition of the laboratory abnormalities, or lack thereof. Another drawback is the descriptive nature of the study, designed to determine whether pediatric cases existed in addition to adult cases; the study was not designed to investigate fully the cases of DKA with concomitant metabolic alkalosis.

Conclusions

A metabolic alkalosis may be present in a number of children and adults with DKA when the serum bicarbonate and pH are relatively normal. An significant difference between the increase in the AG and the decrease in the serum bicarbonate should alert clinicians that more than a simple metabolic acidosis is present, facilitating prompt diagnoses and treatment.

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