Original Article

VENOUS SERUM BICARBONATE CONCENTRATION PREDICTS ARTERIAL PH IN ADULTS WITH DIABETIC KETOACIDOSIS

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ABSTRACT

Objective: The initial assessment of metabolic acidosis in subjects with diabetic ketoacidosis (DKA) is arterial blood gas analysis. This process is expensive, painful, and technically difficult. Furthermore, blood gas analysis may not be available in some facilities, especially in developing countries where DKA-associated morbidity and mortality remain high. Therefore, we investigated the utility of venous bicarbonate concentration obtained from a basic metabolic panel in predicting arterial pH in adults with DKA.

Methods: We performed a retrospective analysis of clinical and biochemical data of 396 adults admitted to 2 community teaching hospitals with DKA. We determined the correlation between arterial pH and venous serum parameters. Using multiple logistic regression, we obtained a predictive formula for arterial pH from serum venous bicarbonate level.

Results: The patient population was 59.0% male and had a mean age of 36.7 ± 13.3 years. We derived that arterial pH = 6.97 + (0.0163 × bicarbonate), and by applying this equation, we determined that serum venous bicarbonate concentration of ≤20.6 mEq/L predicted arterial pH ≤7.3 with over 95% sensitivity and 92% accuracy.

Conclusion: Venous serum bicarbonate obtained from the basic metabolic panel is an affordable and reliable way of estimating arterial pH in adults with DKA. Validation of this formula in a prospective study would offer a more accessible means of estimating metabolic acidosis in adults with DKA, especially in developing countries where DKA incidence and mortality remain high. **(Endocr Pract. 2014;20:201-206)**

Abbreviations:
DKA = diabetic ketoacidosis

INTRODUCTION

Diabetic ketoacidosis (DKA) is a severe metabolic complication of uncontrolled diabetes, the incidence of which continues to rise (1). The economic burden of DKA remains substantial; therefore, it is important to identify measures that will reduce the treatment cost of this potentially fatal condition. DKA is defined by the triad of hyperglycemia, ketonemia, and metabolic acidosis, and the latter is usually assessed by measuring pH of arterial blood (2). However, blood gas analysis requires expensive equipment that may not be available in all facilities, especially in developing countries where DKA morbidity and mortality remain high (3). Furthermore, obtaining arterial blood can be painful and technically difficult. Studies have investigated the use of venous blood to measure metabolic acidosis in subjects with DKA (4-7). Some of these studies have provided conversion factors between arterial and venous pH values (4,5), while others have derived a conversion between arterial and venous bicarbonate levels (7). Others have investigated the prediction of venous pH using venous bicarbonate level in pediatric patients (6). However, estimation of pH requires a blood gas analyzer, which can be expensive and may not be readily available in some centers. Another study investigated the use of beta-hydroxyl butyrate, the predominant ketone body anion in DKA, for the diagnosis of the condition and concluded that

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this metabolite may be a superior measure of acidosis in DKA because it is more specific for DKA than pH, bicarbonate, and anion gap (8). Again, many facilities do not routinely measure beta-hydroxyl butyrate in subjects with DKA. The basic metabolic panel, which is less expensive and more readily available than arterial pH in most facilities, measures critically important electrolytes in patients with DKA, including bicarbonate. Therefore, we investigated the utility of serum venous bicarbonate concentration in estimating arterial pH in adults with DKA.

METHODS

We retrieved the medical records of all subjects aged 18 years or above admitted with DKA in 2 community teaching hospitals: Bronx Lebanon Hospital Center, Bronx, New York (July 2001-June 2004) and The Regional Medical Center, Memphis, Tennessee (October 2003-October 2008). Patients with DKA were identified by applying the International Classification of Diseases, Ninth Revision (ICD-9) code for DKA (250.1) to the hospitals' admission and discharge records. DKA was diagnosed and treated according to American Diabetes Association guidelines (1):

Diagnostic Criteria for DKA

1. Blood glucose level ≥250 mg/dL
2. Ketonemia determined by positive serum nitroprusside reaction ≥moderate
3. Acidosis demonstrated by 1 or more of the following:
   A. Anion gap >12 mEq/L
   B. pH ≤7.30
   C. Serum bicarbonate level <15 mEq/L
4. Ketosis and acidosis could not be due to poisoning, hyperemesis gravidarum, or pre-existing intrinsic renal failure

DKA Treatment

All patients were initially treated in the emergency department and were transferred to the intensive care unit as soon as possible. Intravenous infusion of normal saline was given for fluid repletion and was replaced with dextrose infusion when blood glucose was <200 mg/dL. Each patient was commenced on intravenous regular insulin infusion at the rate of 0.1 unit/kg body weight/hour after an intravenous bolus dose of 0.1 unit/kg given after excluding hypokalemia. Blood glucose was monitored hourly, and the insulin dose was adjusted accordingly to achieve steady hourly reductions in blood glucose of 50 to 70 mg/dL. Serum electrolytes and venous pH were monitored every 2 hours. A chart of the blood glucose, serum electrolytes, venous pH, and fluids administered was maintained. Electrolyte abnormalities, such as hypokalemia, were corrected as indicated. Insulin drip was continued until acidosis and ketosis resolved. As soon as patients could eat, basal insulin was started 2 hours before the regular insulin drip was discontinued. The patients were managed by the intensive care unit team, which consisted of the attending critical care physician and internal medicine residents. An attending endocrinologist reviewed the patients as soon as possible.

Demographic and biochemical data of all patients who fulfilled the inclusion criteria were abstracted in an electronic database, including age, sex, blood gas analysis, serum glucose, bicarbonate, anion gap, sodium, potassium, creatinine, blood urea nitrogen, and serum ketone concentration.

Outcome Measures

The primary outcome measure was to determine the predictors of arterial pH from venous serum chemistry. Secondary measures included correlation of serum venous bicarbonate concentration and anion gap with arterial pH obtained simultaneously on admission in adults with DKA.

Ethical Considerations

The Institutional Review Boards of the 2 hospitals approved this study, and confidentiality was maintained throughout.

Statistical Analysis

The data obtained were summarized as mean ± standard deviation and proportion. Correlation analysis was applied to determine the relationship between arterial blood pH and venous blood analytes. A multiple logistic regression model was used to determine the predictors of arterial pH using different covariates. Statistical significance was set at $P<0.05$ using 2-tailed tests.

RESULTS

A total of 396 patients who fulfilled the inclusion criteria were included in the analysis; 59% of the subjects were males, and the mean age was 36.7 ± 13.3 years. Initial laboratory evaluations revealed significant biochemical perturbations with hyperglycemia, acidosis, ketonemia, hypertonicity, hyperkalemia, and azotemia. The patients' clinical and biochemical data on admission are shown in Table 1. A strong direct linear relationship was found between serum bicarbonate and arterial pH (Pearson correlation coefficient, 0.6; $P<.0001$), while a significant inverse relationship was demonstrated between anion gap and arterial pH (Pearson correlation, –0.38; $P<.0001$) (Fig. 1 *A* and *B*). Similarly, we demonstrated a significant inverse correlation between serum glucose, creatinine, osmolality, and blood urea nitrogen versus arterial pH (Pearson correlations of –0.24, –0.27, –0.19, and –0.20, respectively; $P<.0001$). However, only serum bicarbonate concentration, glucose, and creatinine were independent

predictors of arterial pH in a multivariate analysis; of these 3 covariates, the multiple logistic regression model showed that bicarbonate was the best predictor of arterial pH ($P<.0001$). Anion gap, serum osmolality, serum ketone bodies concentration, potassium, and blood urea nitrogen did not predict arterial pH (Table 2). Using this model, we derived an equation in which arterial pH = 6.97 + (0.0163 × bicarbonate). A serum bicarbonate level ≤20.6 mEql/L predicted arterial pH ≤7.3 with over 95% sensitivity and 92% accuracy. Serum creatinine and glucose were also predictors of arterial pH but to a lesser degree than bicarbonate ($P<.03$ and $<.02$, respectively). Based on the formula above, we generated Table 3 to estimate arterial pH from serum bicarbonate.

Table 1
Patient Demographic and Biochemical Characteristics

Sample size (n)	396
Sex (M/F)	234/162
Age (yrs)	36.7 ± 13.3
Glucose (mg/dL)	645.0 ± 258
pH	7.15 ± 0.13
Bicarbonate (mEq/L)	10.9 ± 5.0
Anion Gap (mEq/L)	24.7 ± 7.4
Osmolality (mOsmol/kg)	307 ± 23
Potassium (mEq/L)	5.2 ± 1.1
Creatinine (mg/dL)	2.0 ± 1.2
Blood urea nitrogen (mg/dL)	26.5 ± 17.8

DISCUSSION

DKA is usually diagnosed by the triad of hyperglycemia, ketonemia/ketonuria, and metabolic acidosis. The initial evaluation of metabolic acidosis in subjects with DKA is usually performed by arterial blood gas analysis. This procedure is invasive, painful, technically difficult, and may not be affordable in many health facilities, especially in developing countries where DKA morbidity and mortality could be high. Therefore, we investigated the value of venous bicarbonate obtained from a basic metabolic panel in predicting arterial pH in adults with DKA. Previous studies have reported on the use of venous blood gas analysis in place of arterial blood gas to measure metabolic acidosis in subjects with DKA (4-7,9). A prospective study of 44 episodes of DKA that simultaneously measured arterial and venous pH on admission found a mean arterial pH of 7.20 compared to a mean venous pH of 7.17; the average difference in pH ranged from 0.0 to 0.11, with a mean of 0.03. (4). In another prospective study that compared simultaneously obtained blood gas and acid-base measurements in arterial and venous blood samples from patients with uremic acidosis and diabetic ketoacidosis in the emergency room, it was concluded that a venous blood sample can be used to evaluate acid-base status in uremic and DKA patients (9).

In addition, a prospective observational study of 200 consecutive patients admitted with DKA in an emergency department investigated the correlation and precision between arterial and venous blood gas values and their utility in making management decisions (10). The authors concluded that venous pH correlated with arterial pH and could serve as a substitute for arterial pH. Furthermore, a review of studies comparing arterial and venous pHs in subjects with DKA and other acidosis-causing conditions reported that the weighted average difference between the two parameters was 0.02, with 95% confidence limits of –0.009 to 0.021 (5). These studies also observed very high concordance and correlation between venous and arterial bicarbonate concentrations (4,5,7). Although using venous blood in place of arterial blood to assess metabolic acidosis in DKA is technically less difficult, it requires a blood gas analyzer, which may be expensive.

We have derived a means of estimating arterial pH from venous bicarbonate level, which is included in the basic metabolic panel. This does not require a blood gas analyzer and would be an affordable and accessible method of evaluating patients with DKA. Our formula predicted arterial pH with sensitivity >95% and 92% accuracy, suggesting that venous pH could be used in place of arterial pH in the initial evaluation of adults with DKA. The findings of our study are consistent with those of another retrospective review of 300 pediatric patients admitted with DKA in the emergency department of a children's hospital. The authors reported a significant linear relationship between venous bicarbonate concentration and venous pH; serum bicarbonate concentration ≤18.5 mEq/L predicted venous pH ≤7.3 with 93% sensitivity and 91% specificity (6). We would like to point out that we found the relationship between arterial pH and venous bicarbonate to be more parabolic than linear (Fig. 1 *C*). The correlation coefficient (*R*) for a parabolic relationship was 0.66 compared to 0.60 for a linear relationship; however, both models were statistically highly significant ($P<.0001$). Therefore, the quadratic formula pH = 6.83 + ([0.044 × bicarbonate] – [0.0011 × bicarbonate^2]) derived from the parabolic relationship should be a more accurate predictor of arterial pH from venous bicarbonate concentration. It is evident that a quadratic formula is more complex than the linear model of pH = 6.97 + (0.0163 × bicarbonate. Considering that both formulae are good and that our overall goal is to simplify DKA management, we elected to use the linear model for our prediction.

It would be pertinent to note that measures of acidosis, such as bicarbonate, anion gap, and pH, are not specific for DKA and could be altered by respiratory compensation to

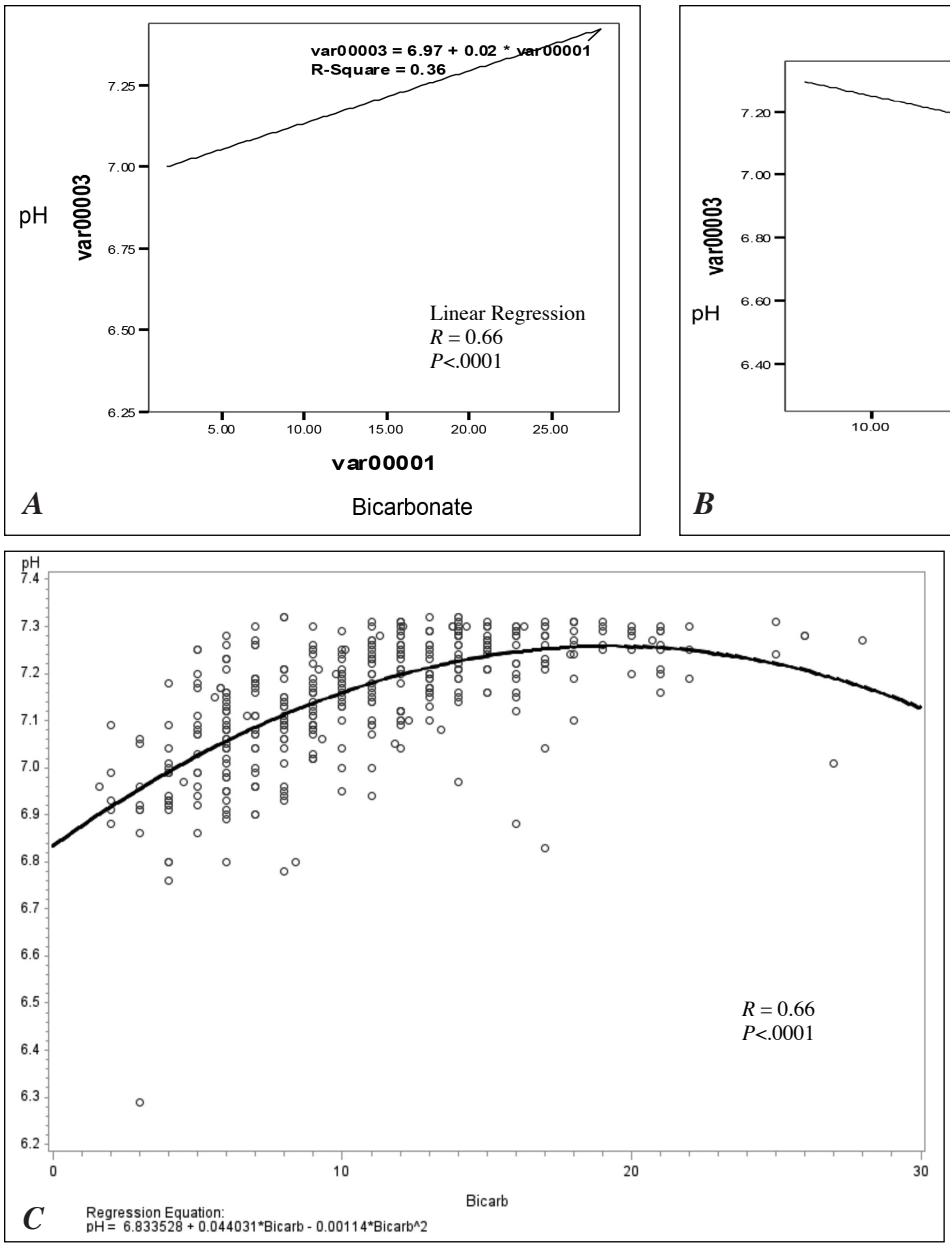

Fig. 1. *A*, Serum bicarbonate versus arterial pH. *B*, Serum anion gap versus arterial pH. *C*, Serum bicarbonate and arterial pH (parabolic relationship).

metabolic acidosis, such as hyperventilation or concomitant respiratory disorder and metabolic alkalosis due to loss of protons as in vomiting, which is a common presentation of DKA or renal disease. Therefore, application of the formula derived from our study should take into consideration the possibility of mixed or complex acid-base disorder in patients with DKA.

Serum anion gap was not an independent predictor of arterial pH in our study. This may be due to the fact that anion gap can be affected by several anions that are not taken into account in computing the anion gap, such as lactate, beta-hydroxybutyrate, acetoacetate, phosphate, and sulfate. Varying ability of the kidney to excrete these anions would result in different anion gap values in individuals with comparable levels of acidosis (11-13). In a study of acid-base patterns in 196 patients admitted with DKA, the authors observed a broad range of disturbances, including pure anion gap metabolic acidosis and pure hyperchloremic acidosis. They reported that the degree of renal dysfunction, which accounted for greater ketone retention, was determined by the severity of dehydration (11). This may explain the significant inverse correlation between serum creatinine concentration and arterial pH observed in this study. We did not find a correlation between serum ketone bodies concentration and arterial pH, which couldbe explained by the fact that our evaluation was done using the nitroprusside method, which does not measure beta-hydroxybutyrate, the predominant ketone body in

Table 2
Multiple Regression of Predictors of pH

Predictor	Parameter estimate	Standard error	*t*	*P*
Bicarbonate	0.01567	0.0014	11.15	<.0001
Creatinine	–0.01329	0.0064	–2.19	.029
Glucose	–0.000082	0.0000	–2.35	.019
Anion gap	0.0008	0.0010	0.78	.438
Osmolality	0.00022	0.0003	0.70	.485
Ketones	–0.00364	0.0073	–0.50	.620
Potassium	–0.0086	0.0058	–1.48	.140
Blood urea nitrogen	0.00019	0.0004	0.44	.658

DKA. It is noteworthy that another study that investigated the use of beta-hydroxybutyrate for the diagnosis of DKA found a significant correlation between serum bicarbonate concentration and beta-hydroxybutyrate and concluded that this metabolite may be a superior measure of acidosis in DKA because it is more specific for DKA than pH, bicarbonate, and anion gap (8). A recent study investigated the contribution of D-lactate, a metabolite that is not routinely measured in patients with DKA, and found that D-lactate was markedly elevated in subjects with DKA compared to normal subjects and diabetic patients without DKA (14). Furthermore, blood levels of D-lactate significantly correlated with acidosis and anion gap. The correlations of hyperglycemia, azotemia, and hypertonicity with arterial pH observed in the present study are consistent with the known pathophysiology of DKA. Insulinopenia and elevated counterregulatory hormones result in accelerated gluconeogenesis, lipolysis, ketogenesis, osmotic diuresis, and dehydration (15,16). However, an earlier report on the relationship between hyperglycemia severity and metabolic acidosis in DKA found no correlation between these 2 biochemical measurements (17).

The current American Diabetes Association guidelines recommend a serum bicarbonate concentration ≤15 to 18 mEq/L as the cutoff for the diagnosis of DKA (2). However, as shown in Table 3, this bicarbonate level represents a pH level that is lower than 7.3, suggesting a higher degree of acidosis. In centers where blood gas analysis may not be available, serum bicarbonate concentration of ≤20 mEq/L may represent a more accurate diagnostic cutoff for DKA, which corresponds to an arterial pH of 7.3.

Table 3
Bicarbonate Concentration and Predicted pH Level

Venous bicarbonate (mEq/L)	Predicted arterial pH
5.0	7.05
7.5	7.09
10.0	7.13
12.5	7.17
15.0	7.21
17.5	7.26
20.0	7.30
22.5	7.34
25.0	7.38
27.5	7.42
30.0	7.46

CONCLUSION

We performed a retrospective analysis of a large cohort of adults with DKA to derive a formula for estimating arterial pH from venous bicarbonate levels with a sensitivity >95% and an accuracy of 92%. This method does not require a blood gas analyzer and is a more affordable and accessible method for evaluating patients with DKA. Validation of this finding in a prospective study would provide a less expensive alternative for assessing metabolic acidosis in adults with DKA, especially in developing countries where the incidence and mortality of DKA remain high.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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