

# Acidosis: The Prime Determinant of Depressed Sensorium in Diabetic Ketoacidosis

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**OBJECTIVE**— The etiology of altered sensorium in diabetic ketoacidosis (DKA) remains unclear. Therefore, we sought to determine the origin of depressed consciousness in DKA.

**RESEARCH DESIGN AND METHODS**— We analyzed retrospectively clinical and biochemical data of DKA patients admitted in a community teaching hospital.

**RESULTS**— We recorded 216 cases, 21% of which occurred in subjects with type 2 diabetes. Mean serum osmolality and pH were  $304 \pm 31.6$  mOsm/kg and  $7.14 \pm 0.15$ , respectively. Acidosis emerged as the prime determinant of altered sensorium, but hyperosmolality played a synergistic role in patients with severe acidosis to precipitate depressed sensorium (odds ratio 2.87). Combination of severe acidosis and hyperosmolality predicted altered consciousness with 61% sensitivity and 87% specificity. Mortality occurred in 0.9% of the cases.

**CONCLUSIONS**— Acidosis was independently associated with altered sensorium, but hyperosmolality and serum “ketone” levels were not. Combination of hyperosmolality and acidosis predicted altered sensorium with good sensitivity and specificity.

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**D**iabetic ketoacidosis (DKA) is frequently associated with altered mental status, which is correlated with the severity of the disease and prognosis (1). However, the etiology of depressed sensorium in DKA remains uncertain and controversial (2,3). Putative factors in the pathogenesis of diabetic ketoacidotic coma include cerebral hypoperfusion due to circulatory collapse and cerebral thrombosis (4), reduced cerebral glucose and oxygen utilization (1,5), acidosis (6,7), hyperosmolality (8,9), and direct toxic effect of ketone bodies (2). Cerebral edema remains an important precipitant of altered consciousness in DKA, especially in children.

Different studies have yielded conflicting results regarding the role of these etiologic factors in the pathogenesis of al-

tered mentation in patients with DKA. Hence, the origin of clouded sensorium in DKA remains to be fully elucidated. We undertook to study the etiology of depressed consciousness in patients admitted with DKA at the Regional Medical Center in Memphis.

## RESEARCH DESIGN AND METHODS

We performed a retrospective analysis of patients admitted with DKA between October 2003 and October 2008. DKA was diagnosed based on American Diabetes Association criteria (10). Demographic and biochemical data were extracted from the medical records of the patients including serum pH, bicarbonate, sodium, potassium, blood urea nitrogen (BUN), serum creatinine, osmolality, “ketones,” arterial pO<sub>2</sub> and pCO<sub>2</sub>,

as well as level of consciousness. Serum effective osmolality was calculated as reported before (10).

Patients were categorized by mental status into alert versus altered (semi-comatose and comatose).

## Statistical analysis

For comparison of variables among groups, univariate analysis was performed. To identify the independent determinants of level of consciousness, multivariate linear model analysis was applied. The groups were characterized using means  $\pm$  SD and compared by Student's *t* test for continuous variables and  $\chi^2$  test for discrete variables using SAS 9.1.3 software. Using quartiles of pH and serum osmolality as predictors of depressed consciousness, we generated a receiver operating characteristic curve from which we derived the sensitivity and specificity of these independent variables in predicting the presence of depressed sensorium in patients presenting with DKA.

Quartiles of pH were as follows: 6.92–7.03, 7.04–7.15, 7.16–7.25, and 7.26–7.40, while quartiles of serum osmolality were as follows: 231–287, 287.4–301, 301.2–315, and 316–431.

The Institution Review Board of the University of Tennessee Health Science Center approved this study.

**RESULTS**— We recorded 216 cases of DKA in patients aged  $37.7 \pm 12.4$  years, 57.9% of whom were males, whereas 21 and 15% had type 2 diabetes and new-onset diabetes, respectively. Average blood glucose level was  $658.6 \pm 276.0$  mg/dl, whereas mean serum osmolality and pH were  $304 \pm 31.6$  mOsm/kg and  $7.14 \pm 0.15$ , respectively. Serum sodium and potassium were  $131.6 \pm 6.5$  and  $5.4 \pm 3.5$  mEq, respectively. The clinical and biochemical characteristics of the patients according to mental status are shown in Table 1. Variables that demonstrated a significant difference between the two groups were entered into a multiple regression model shown in supplemental Table 1 (available in an online appendix at <http://care.diabetesjournals.org>).

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Table 1—Clinical and biochemical characteristics of the patients at presentation

	Mental status		P
	Alert	Altered	
n	133	83	
Age (years)	37.1 ± 13.1	38.6 ± 11.5	0.41
Sex			0.05
Male	70	55	
Female	63	28	
Race			0.39
African American	116	71	
Caucasian	16	7	
Hispanic	2	1	
Others	3	0	
Type of diabetes			0.12
Type 1	94	45	
Type 2	24	21	
New-onset	24	8	
Systolic blood pressure	130 ± 21	122 ± 27	0.022*
Diastolic blood pressure	73 ± 18	70 ± 18	0.023*
Leucocytes	13.4 ± 6.7	17.1 ± 8.6	0.001*
Glucose	603 ± 236	747 ± 311	0.0004*
Serum ketones			0.06
Mild	46	20	
Moderate	68	43	
Large	16	19	
Blood pH	7.19 ± 0.10	7.05 ± 0.16	<0.0001*
Serum bicarbonate	11.8 ± 4.3	8.8 ± 4.7	<0.0001*
Anion gap	22.8 ± 6.7	29.8 ± 32.4	0.062
Serum osmolality	300.1 ± 18.0	310.8 ± 45.0	0.041*
Serum sodium	131.8 ± 6.2	131.2 ± 6.9	0.49
Serum potassium	5.1 ± 1.2	6.0 ± 5.5	0.14
Blood urea nitrogen	23.8 ± 16.8	33.8 ± 22.6	0.0007*
Serum creatinine	2.3 ± 1.1	3.1 ± 2.3	0.003*
pCO <sub>2</sub>	50.0 ± 35.4	47.4 ± 38.5	0.61
pO <sub>2</sub>	79.1 ± 52.8	88.3 ± 65.3	0.28

\*Statistically significant.

org/cgi/content/full/dc10-0102/DC1). As can be seen, only pH emerged as an independent determinant of level of consciousness in this cohort of patients with DKA.

To further elucidate the influence of acidosis measured by arterial pH and effective serum osmolality on the level of consciousness at presentation, we determined the odds ratio of depressed sensorium in all 216 subjects by quartiles of pH and osmolality (see supplemental Fig. 1 in the online appendix). Supplemental Fig. 1 clearly demonstrates that arterial pH is the prime determinant of mental status in DKA, which appeared to act synergistically with hyperosmolality to produce depressed consciousness. In patients with severe acidosis (lowest pH quartile ≤7.03), the odds ratio for altered sensorium was 1 if serum osmolality was in the

lowest quartile (≤287), but increased almost threefold to 2.8 among patients in the highest quartile of osmolality (≥316). However, in the absence of severe acidosis, worsening hyperosmolality was not significantly associated with altered sensorium (odds ratio <1). Therefore, although acidosis was required for depressed sensorium to occur, the likelihood of altered mentation was higher in the presence of elevated serum osmolality. A total of 45 patients (20.8%) were in the lowest pH quartile, while 52 patients (24.1%) were in the highest osmolality quartile (≥316 mOsm/kg). Fifteen subjects (6.9%) had a combination of low pH and high osmolality. This latter category represented the patients with the highest likelihood of having depressed level of consciousness (odds ratio 2.81). Mortality, which was recorded in 0.9% of the

cases, occurred in patients who had presented with severe acidosis and sepsis. The combination of severe acidosis and hyperosmolality predicted altered sensorium with sensitivity of 61% and specificity of 87% (supplemental Table 2 and supplemental Fig. 2).

**CONCLUSIONS**— We have demonstrated that acidosis measured by arterial pH at presentation is the prime determinant of mental status in DKA. Severe acidosis appeared to act in concert with hyperosmolality in a synergistic manner to produce depressed sensorium in these patients. Therefore, a combination of acidosis and hyperosmolality at presentation may identify a subset of patients with severe DKA (7% in this study) who may benefit from more aggressive treatment and monitoring. Identifying this class of patients, who are at a higher risk for poorer prognosis, may be helpful in triaging them, thus further improving the outcome.

The dominant effect of acidosis on mental status obtained in this study is consistent with the findings of other clinical studies (6,7).

Some studies have reported that depressed sensorium in DKA is attributable to elevated serum osmolality (8,9). However, despite some biochemical similarities between these two hyperglycemic crises, there are notable differences that may suggest different pathogenic mechanisms. We observed that hyperosmolality, which was associated with depressed sensorium in a univariate model, did not prove to be an independent predictor of altered sensorium in a multivariate analysis. However, in the presence of hypertonicity, the likelihood of altered mental status was increased in patients with severe acidosis. Studies that reported hyperosmolality as the sole etiology of altered consciousness DKA did not perform logistic regression (8) as we have done. This could be a confounding factor, since up to 30% of patients with DKA may have high serum osmolality (9,11).

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