

# Prolonged QT Interval Corrected for Heart Rate During Diabetic Ketoacidosis in Children

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**Objective:** To evaluate the effect of diabetic ketoacidosis (DKA) on the QT interval corrected for heart rate (QTc) in children. Ketosis occurs in several conditions, including DKA and alcoholic ketoacidosis, and during use of very low-carbohydrate diets. Prolongation of the QTc has been described in a few children receiving ketogenic diets, but cardiac effects of ketosis have not otherwise been investigated.

**Design:** For this observational study, we performed electrocardiography during DKA and after recovery. We measured QTc as the QT interval divided by the square root of the R-R interval and correlated QTc with clinical variables.

**Setting:** The pediatric emergency department and intensive care unit of an academic medical center.

**Patients:** Thirty children with type 1 diabetes mellitus and DKA.

**Main Outcome Measure:** The QTc during DKA.

**Results:** The mean (SD) QTc during DKA was 450 (38) milliseconds (range, 378-539 milliseconds). After recovery from DKA, the mean (SD) QTc decreased to 407 (36) milliseconds (range, 302-485 milliseconds; difference, 43 milliseconds; 95% confidence interval, 23-63 milliseconds) ( $P < .001$ ). Fourteen of the 30 children (47%) had prolonged QTc during DKA (range, 450-539 milliseconds). After recovery from DKA, only 4 children (13%) had persistent QTc prolongation (range, 451-485 milliseconds). The anion gap was significantly associated with QTc prolongation (correlation coefficient, 0.49;  $P = .006$ ). Most patients had no electrolyte abnormalities or hypoglycemia to account for QTc prolongation.

**Conclusions:** Prolonged QTc occurs frequently during DKA and is correlated with ketosis. Current guidelines regarding cardiac monitoring of children during DKA should be strictly followed, and electrocardiographic screening of patients with other ketotic conditions should be considered.

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**C**ARDIAC ARRHYTHMIAS AND cardiac arrest have been described in children with diabetic ketoacidosis (DKA).<sup>1-3</sup> These rare complications of DKA generally have been attributed to electrolyte abnormalities during DKA treatment. Case reports, however, describe prolongation of the QT interval corrected for heart rate (QTc) in children receiving ketogenic diets in the absence of electrolyte abnormalities.<sup>4</sup> In these children, there was a positive correlation between QTc prolongation and  $\beta$ -hydroxybutyrate concentrations and between QTc prolongation and systemic acidosis. Prolonged QTc and/or sudden death presumed to be caused by cardiac arrhythmias has also been described in adolescents and adults using very-low-carbohydrate, calorie-restricted diets.<sup>5-8</sup> Likewise, sudden death has been documented in adults with alcoholic ketoacidosis.<sup>9</sup>

The consistent association between various ketotic conditions and prolonged QTc and/or sudden death raises the question of whether ketosis may directly affect cardiac repolarization. In this study, we tested the hypothesis that QTc prolongation occurs in children during DKA and returns to normal with resolution of ketosis. We also assessed correlations of clinical and biochemical variables with QTc prolongation.

## METHODS

### STUDY POPULATION

Patients were eligible for participation in the study if they were younger than 18 years, had been diagnosed as having type 1 diabetes mellitus, and had DKA, defined as a serum glucose level of greater than 300 mg/dL, venous pH of less than 7.25 and/or a serum bicarbonate level of less than 15 mEq/L, and a positive test re-

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sult for urine ketones or a serum ketone level of greater than 3 mmol/L. Patients were ineligible if they were taking medications known to affect QTc or if they had other underlying conditions known to affect QTc. (To convert glucose to millimoles per liter, multiply by 0.0555; and bicarbonate to millimoles per liter, by 1.0.)

### DKA TREATMENT PROTOCOL

The study was approved by the institutional review board of the participating institution. A convenience sample of patients was enrolled into the study after written informed consent was obtained from parents or guardians. We treated enrolled patients according to a standardized DKA protocol. All patients received an initial infusion of 10 to 20 mL/kg of 0.9% isotonic sodium chloride solution, depending on the assessed degree of hypovolemia. Patients with persistently poor perfusion or hemodynamic instability after the initial fluid infusion were given additional infusions of 0.9% isotonic sodium chloride solution until normal perfusion and hemodynamic stability were established. Subsequent intravenous fluids were administered as 0.67% isotonic sodium chloride solution (sodium concentration, 112 mEq/L) with the rate calculated to replace an estimated deficit of 70 mL/kg spread across 48 hours. Insulin was administered via continuous intravenous infusion at an initial rate of 0.1 U/kg/h. Patients were not treated with bicarbonate. Potassium replacement therapy was initiated with intravenous fluid containing potassium chloride, 20 mEq/L, and potassium phosphate, 20 mEq/L, with the dosage adjusted to maintain serum potassium concentrations within the reference range. Glucose was added to the intravenous fluids when the serum glucose concentration was less than 300 mg/dL. For patients referred from outside hospitals, we changed to our treatment protocol on their arrival to the pediatric intensive care unit.

### ELECTROCARDIOGRAPHY PROTOCOL

Each patient had an initial electrocardiogram (ECG) recorded during DKA. A second ECG was recorded after recovery from DKA (defined as a serum bicarbonate concentration of > 18 mEq/L). Follow-up ECGs were recorded at the time of hospital discharge, or at the patient's first outpatient visit after discharge from the hospital (median, 45 days after the initial ECG; range, 24 hours to 180 days). A standard 12-lead ECG was recorded at 25 mm/s, along with a lead II rhythm strip recorded at 50 mm/s. The QT and R-R interval measurements were recorded from each ECG by a single pediatric cardiologist/electrophysiologist (J.P.) who was masked to the patients' clinical and biochemical data. The QT interval was measured from the onset of the QRS complex to the end of the T wave. The end of the QT interval was defined as the intersection of a tangent to the steepest downslope of the dominant repolarization wave with the isoelectric line. The QTc was calculated according to the Bazett formula as the QT interval divided by the square root of the R-R interval, where the R-R interval is measured in relation to the previous QRS complex.<sup>10</sup> Three separate measurements by the same pediatric cardiologist/electrophysiologist were obtained from each ECG, and the mean of these measurements was used as the value for the QTc. Lead II was used preferentially for QTc measurement.<sup>11</sup> If a T wave could not be clearly discerned in lead II, then the next limb lead with a clearly discernible T wave was used. Prolongation of QTc was defined as a QTc of at least 450 milliseconds. To evaluate interobserver agreement, QTc measurements were repeated by a second cardiologist/electrophysiologist (K.G.) who was masked to the clinical and biochemical patient data and to the ECG measurements of the first cardiologist. These repeated QTc measurements by a second cardiologist were used for evaluation of interobserver agreement only. The initial QTc measure-

**Table 1. Clinical and Biochemical Data in 30 Children With Type 1 Diabetes Mellitus and DKA<sup>a</sup>**

Variable	At Presentation	At Time of Initial ECG
Age, y	11.4 (3.6)	
Male, No. (%)	12 (40)	
New onset of diabetes, No. (%)	15 (50)	
Serum glucose level, mg/dL	671 (282)	342 (163)
Serum sodium level, mEq/L	133 (5)	138 (7)
Serum potassium level, mEq/L	4.8 (0.9)	4.1 (0.9)
Serum bicarbonate level, mEq/L	9 (3)	10 (4)
Venous pH	7.07 (0.08)	7.17 (0.10)
Pco <sub>2</sub> , mm Hg	25 (8)	26 (7)
Serum calcium level, mg/dL	9.9 (0.9)	9.4 (0.7)
Serum magnesium level, mg/dL	2.5 (0.5)	2.2 (0.5)
Serum phosphorus level, mg/dL	5.0 (1.7)	3.7 (1.6)

Abbreviations: DKA, diabetic ketoacidosis; ECG, electrocardiogram.

SI conversion factors: To convert bicarbonate to millimoles per liter, multiply by 1.0; calcium to millimoles per liter, by 0.25; glucose to millimoles per liter, by 0.0555; magnesium to millimoles per liter, by 0.411; phosphorus to millimoles per liter, by 0.323; potassium to millimoles per liter, by 1.0; and sodium to millimoles per liter, by 1.0.

<sup>a</sup>Unless otherwise indicated, data are expressed as mean (SD).

ments by the primary study pediatric cardiologist were used in all subsequent analyses.

### STATISTICAL ANALYSIS

We compared QTc measurements during DKA with QTc measurements after recovery from DKA using the Wilcoxon signed rank test. We compared clinical and biochemical findings for patients with and without QTc prolongation using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. For these comparisons, we calculated the anion gap as  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ , where  $\text{Na}^+$  indicates sodium;  $\text{Cl}^-$ , chloride; and  $\text{HCO}_3^-$ , bicarbonate. We used the weighted  $\kappa$  statistic to assess interobserver agreement in QTc measurement (rounded to 2 decimal places) between the 2 study cardiologists.<sup>12</sup> We also evaluated the association between the anion gap and QTc after adjusting for age and heart rate using linear regression. We performed a similar analysis to adjust for serum potassium and calcium concentrations at the time of the ECG. We considered  $P < .05$  to represent statistical significance. Unless otherwise indicated, data are expressed as mean (SD).

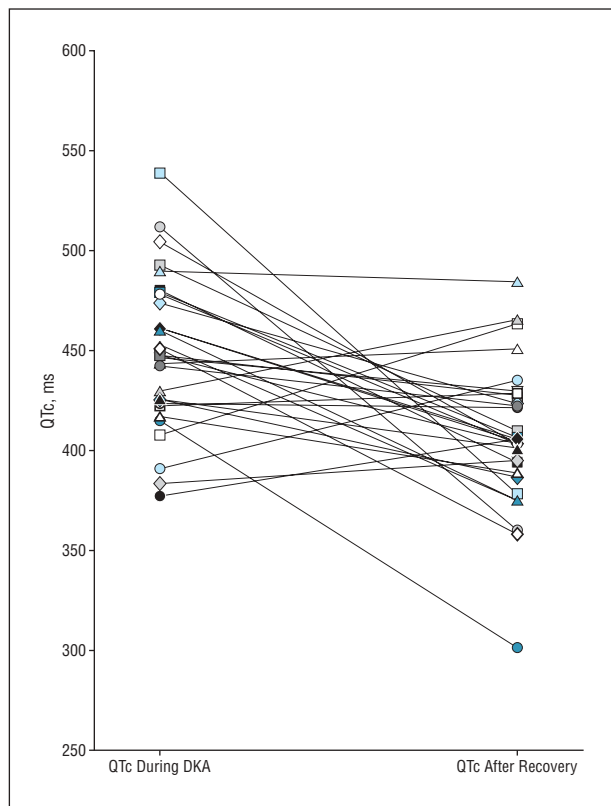
### CONVERSION FACTORS

To convert bicarbonate to millimoles per liter, multiply by 1.0; calcium to millimoles per liter, multiply by 0.25; glucose to millimoles per liter, multiply by 0.0555; and potassium to millimoles per liter, multiply by 1.0.

## RESULTS

In 30 children, QTc was measured during and after DKA (**Table 1**). Fifteen of these children had new onset of type 1 diabetes mellitus, and the other 15 had known type 1 diabetes. The ECG measurements were recorded a mean of 6.2 (5.0) hours after the initiation of treatment for DKA.

The mean QTc for these 30 children during DKA was 450 (38) milliseconds (range, 378-539 milliseconds)



**Figure 1.** Measurements of the QT interval corrected for heart rate (QTc) in 30 children during diabetic ketoacidosis (DKA) and after recovery.

**Table 2. Clinical and Biochemical Values at Presentation of Patients With and Without QTc Prolongation During DKA<sup>a</sup>**

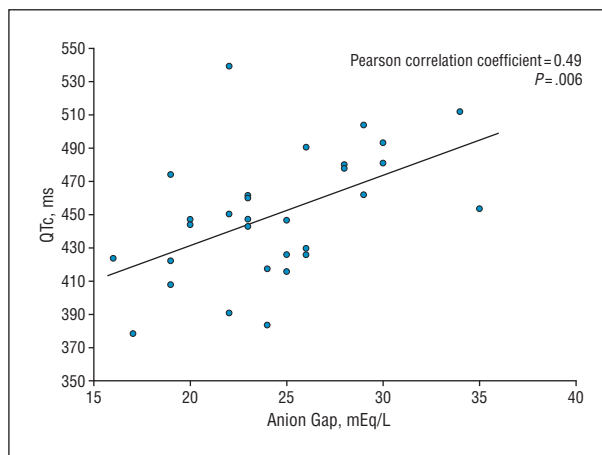
Variable	Long QTc (n=14)	Normal QTc (n=16)	P Value
Age, y	12.3 (2.9)	10.7 (4.1)	.25
New onset of diabetes, No. (%)	7 (50)	8 (50)	>.99
Heart rate, beats/min			
At presentation	136 (16)	118 (24)	.03
At time of ECG	128 (15)	112 (27)	.08
Serum glucose level, mg/dL			
At presentation	692 (259)	653 (308)	.71
At time of ECG	363 (187)	323 (143)	.53
Venous pH			
At presentation	7.06 (0.09)	7.08 (0.07)	.56
At time of ECG	7.16 (0.10)	7.19 (0.10)	.45
Anion gap, mEq/L <sup>b</sup>			
At presentation	27 (5)	22 (3)	.008
At time of ECG	16 (5)	16 (4)	.84
Serum potassium level, mEq/L			
At presentation	4.7 (0.8)	4.8 (1.0)	.64
At time of ECG	3.9 (0.8)	4.2 (1.0)	.29
Serum calcium level, mg/dL			
At presentation	10.0 (0.8)	9.7 (1.0)	.37
At time of ECG	9.5 (0.6)	9.3 (0.8)	.61
Serum magnesium level, mg/dL			
At presentation	2.5 (0.7)	2.4 (0.3)	.66
At time of ECG	2.3 (0.7)	2.1 (0.3)	.58

Abbreviations: DKA, diabetic ketoacidosis; ECG, electrocardiogram; QTc, QT interval corrected for heart rate.

SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; glucose to millimoles per liter, by 0.0555; magnesium to millimoles per liter, by 0.411; and potassium to millimoles per liter, by 1.0.

<sup>a</sup>Unless otherwise indicated, data are expressed as mean (SD).

<sup>b</sup>Calculated as  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ , where  $\text{Na}^+$  indicates sodium;  $\text{Cl}^-$ , chloride; and  $\text{HCO}_3^-$ , bicarbonate.



**Figure 2.** Correlation of serum anion gap with the QT interval corrected for heart rate (QTc) during diabetic ketoacidosis. Anion gap is calculated as  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ , where  $\text{Na}^+$  indicates sodium;  $\text{Cl}^-$ , chloride; and  $\text{HCO}_3^-$ , bicarbonate. The solid line represents the linear regression fit across all subjects. The correlation coefficient and *P* value are shown.

(**Figure 1**). After recovery from DKA, the mean QTc decreased to 407 (36) milliseconds (range, 302-485 milliseconds; difference, 43 milliseconds; 95% confidence interval [CI], 23-63 milliseconds) ( $P < .001$ ). Fourteen of the 30 children (47%) had QTc measurements of 450 milliseconds or longer during DKA (range, 450-539 milliseconds).

After recovery from DKA, only 4 children (13%) had persistent QTc of 450 milliseconds or longer, and the degree of prolongation was mild (range, 451-485 milliseconds). Two of these 4 children had ECGs repeated several weeks after recovery from DKA, and in both cases the QTc was less than 450 milliseconds. The other 2 patients were lost to follow-up before the ECGs could be repeated in the outpatient setting. None of the children enrolled in the study experienced cardiac arrhythmias during DKA treatment. Determination of QTc by the second cardiologist showed substantial interobserver agreement with the first cardiologist (weighted  $\kappa$ , 0.62; 95% CI, 0.43-0.80;  $P < .001$ ).<sup>12</sup>

Prolongation of QTc occurred with equal frequency among children with new-onset diabetes and those with known diabetes (**Table 2**). The anion gap at presentation was significantly higher in children with QTc prolongation than in those without ( $P = .008$ ). In addition, the initial anion gap was significantly correlated with QTc values during DKA (correlation coefficient, 0.49;  $P = .006$ ), suggesting a strong association between ketosis and QTc prolongation (**Figure 2**). In contrast, the anion gap at the time of ECG recording was not significantly correlated with QTc. There were no other significant differences in biochemical or clinical variables between the 2 groups (**Table 2**).

Age-adjusted blood pressure values were normal in all children throughout the study, and no study participant experienced hypoxia. None of the children had hypoglycemia (defined as a blood glucose concentration of  $< 70$  mg/dL) at the time of recording of the ECG. Hypokalemia (defined as a serum potassium concentration of  $< 3.3$  mEq/L) was present in 5 children at the time of ECG recording (range, 2.4-3.2 mEq/L). Three of these 5

children had serum potassium concentrations of 3.2 mEq/L, just slightly below the reference range. Four of the 5 children with hypokalemia at the time of ECG had a QTc of at least 450 milliseconds. Six children had low serum calcium concentrations (<8.8 mg/dL) at the time of ECG recording (range, 7.9-8.6 mg/dL). Two of these 6 children had a QTc of at least 450 milliseconds. Serum magnesium concentrations were within the reference range in all patients at the time of ECG recording. The QTc measurements were not significantly correlated with the serum potassium concentrations (correlation coefficient, -0.15;  $P=.44$ ), the serum calcium concentration (correlation coefficient, 0.12;  $P=.58$ ), or the serum magnesium concentration (correlation coefficient, 0.02;  $P=.93$ ) at the time of ECG. To further adjust for any effects of electrolyte concentrations on QTc, we conducted a multiple linear regression analysis that included the initial anion gap and the serum potassium and calcium concentrations at the time of ECG as covariates. In this analysis, only the initial anion gap was significantly associated with QTc ( $P=.04$ ) (**Table 3**).

The patients' heart rates were on average more rapid during DKA than after recovery. Because some studies suggest that formulas used to calculate the QTc are inexact,<sup>13,14</sup> we conducted further analyses to assess any residual correlation between heart rate and QTc. In univariate analyses, heart rate was not significantly correlated with QTc during DKA (correlation coefficient, 0.23;  $P=.25$ ) or after recovery (correlation coefficient, 0.32;  $P=.11$ ). To further adjust for any effect of heart rate on QTc not captured in the formulas, we conducted a multiple linear regression analysis that included heart rate, age, and anion gap as covariates, with QTc duration as the outcome variable. The anion gap remained significantly associated with QTc ( $P=.04$ ), but heart rate was not ( $P=.13$ ), suggesting that QTc measurements and their association with the anion gap were not significantly biased by heart rate differences.

#### COMMENT

Prolongation of the QT interval is a serious condition that provides the substrate for development of the potentially life-threatening arrhythmia torsade de pointes.<sup>15</sup> In the present study, we demonstrate that QTc prolongation is present in almost half of children with DKA. After recovery from the DKA episode, QTc was documented to be normal in all but 2 patients (who were lost to follow-up). Most patients had no evidence of electrolyte abnormalities or hypoglycemia to account for the observed QTc prolongation, suggesting that ketoacidosis per se might lead to delayed cardiac repolarization.

Arrhythmia and cardiac arrest are rare complications of DKA and generally have been presumed to be caused by electrolyte abnormalities.<sup>1,2</sup> However, the QTc prolongation observed in the present study might also play a role in these complications, or QTc prolongation due to ketoacidosis might make children more prone to arrhythmias when hypokalemia, hypocalcemia, or hypomagnesemia are superimposed. In addition, sudden death during sleep in children and young adults with type 1

**Table 3. Multivariate Analysis of Biochemical Factors Associated With QTc Prolongation During DKA**

Variable	Coefficient (95% CI)	P Value
Initial anion gap	3.94 (0.14 to 7.74)	.04
Serum calcium level at time of ECG	2.33 (-22.8 to 27.4)	.85
Serum potassium level at time of ECG	-6.87 (-29.0 to 15.2)	.52

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; ECG, electrocardiogram; QTc, QT interval corrected for heart rate.

diabetes mellitus ("dead in bed" syndrome) has been described. This phenomenon has been attributed to hypoglycemia leading to prolonged QTc<sup>16,17</sup>; however, data from the present study raise the question of whether ketosis might also be a factor involved in some of these deaths.

In addition to the present data, studies of other ketotic conditions provide evidence supporting the association between ketosis and QTc prolongation. Deaths have been reported in patients receiving ketogenic diets for the treatment of seizure disorders, but the causes of these deaths have been unclear.<sup>18</sup> One previous case series showed QTc prolongation in 3 of 20 children adhering to a ketogenic diet for management of seizures.<sup>4</sup> The QTc measurements in the 20 children enrolled in that study were found to correlate with  $\beta$ -hydroxybutyrate and serum bicarbonate concentrations. Sudden death has also been described in adults with alcoholic ketoacidosis.<sup>9,19</sup> Although these deaths are generally attributed to hypoglycemia, the present data raise the question of whether ketosis might also play a role. Finally, QTc prolongation and/or sudden death have been documented in adults and adolescents adhering to very-low-calorie, carbohydrate-restricted diets for weight loss.<sup>5-8</sup> Many of these patients had no electrolyte abnormalities to account for QTc prolongation or arrhythmias, and sudden death has been attributed to myocardial atrophy caused by protein and micronutrient deficiencies and to other causes. Our study raises the question of whether ketosis may also play a role in these deaths.

Children with long-standing diabetes but without DKA have been shown to have a longer QTc and a greater frequency of other abnormalities in cardiac autonomic function compared with age-matched control subjects.<sup>20-22</sup> These abnormalities are thought to be manifestations of diabetic neuropathy. In the present study, QTc prolongation could not be attributed to preexisting manifestations of diabetic neuropathy because the QTc returned to normal after recovery from DKA in most of the children. In addition, the frequency of QTc prolongation was equivalent in patients with new-onset diabetes and those with known diabetes.

In the study cited previously<sup>4</sup> describing children receiving a ketogenic diet, QTc measurements correlated with  $\beta$ -hydroxybutyrate measurements and serum bicarbonate concentrations, suggesting a direct relationship between ketosis and QTc prolongation. In the present study, serum ketone concentrations were not measured; however, the anion gap was significantly greater at presentation in children with a prolonged QTc. In ad-

dition, there was a significant positive correlation between QTc values during DKA and the initial anion gap. In the setting of DKA, the anion gap is mainly a reflection of ketosis.<sup>23</sup> Therefore, these findings further support the possibility that ketosis may have a direct effect on the myocardium, causing QTc prolongation.

The anion gap at the time of ECG recording was not significantly associated with QTc, despite the very strong association between the initial anion gap and QTc. The reason for these findings is uncertain; however, it is possible that the effects of ketosis may persist for some time after serum ketone concentrations decrease. Alternatively, if  $\beta$ -hydroxybutyrate is primarily responsible for the observed changes in QTc, the association between the anion gap and QTc might be eliminated during therapy for DKA as  $\beta$ -hydroxybutyrate is converted to acetoacetate.

This study has several limitations. Serum  $\beta$ -hydroxybutyrate and acetoacetate concentrations were not measured, and therefore direct correlations between serum ketone concentrations and QTc prolongation could not be verified. Although the anion gap in DKA is indicative of ketosis, it does not differentiate between  $\beta$ -hydroxybutyrate and acetoacetate concentrations. In addition, although the present study shows an association between ketosis and QTc prolongation, it does not provide any insights into the pathogenesis of QTc prolongation in this setting. Although we did not detect any association between serum electrolyte concentrations and QTc, variations in intracellular ion concentrations caused by DKA may play a role. Similarly, we cannot exclude the possibility that other physiological alterations associated with DKA may play a role, such as central nervous system dysfunction caused by DKA or alterations in sympathetic tone. Finally, the patients' heart rates during the 2 ECG evaluations were usually not equivalent, and many patients had tachycardia during DKA. It has been suggested that currently available formulas for correcting QT interval measurements for heart rate are imperfect and that some residual correlation between heart rate and QT interval may persist, despite the application of formulas for correction.<sup>13,14</sup> In addition, there is disagreement regarding the precise cutoff value defining QTc prolongation.<sup>24,25</sup> It is possible, therefore, that the proportion of patients with QTc prolongation during DKA may be somewhat lower or higher than that documented in our study. It is highly unlikely, however, that tachycardia during DKA is the sole or even a main factor responsible for QTc prolongation during DKA because subanalyses did not demonstrate a significant correlation between heart rate and QTc and because multivariate analyses demonstrated a persistent significant association between the anion gap and QTc prolongation, after adjusting for age and heart rate.

The present study has several possible implications. Although it is not certain that fatal events during DKA are caused by QTc prolongation, our findings suggest that cardiac monitoring of children with DKA is important, and investigation of QTc in other ketotic conditions should be considered. Current consensus statements recommending continuous cardiac monitoring of children with DKA should be strictly followed.<sup>26</sup> In addition, the absence of ketosis should be ensured when using QTc

to evaluate autonomic dysfunction as a manifestation of diabetic neuropathy. Finally, several very low-carbohydrate diets that have recently been popularized for weight loss often induce ketosis.<sup>27</sup> These diets have been recommended for children with severe obesity.<sup>28</sup> Further study is necessary to determine whether individuals with an underlying genetic predisposition toward delayed cardiac repolarization may have greater prolongation of QTc when adhering to such diets or whether healthy individuals who become more markedly ketotic while following these diets may have prolonged QTc.

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**Author Contributions:** Drs Kuppermann and Glaser had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kuppermann and Glaser. *Acquisition of data:* Kuppermann, Park, Glatter, Marcin, and Glaser. *Analysis and interpretation of data:* Kuppermann and Glaser. *Drafting of the manuscript:* Kuppermann and Glaser. *Critical revision of the manuscript for important intellectual content:* Park, Glatter, and Marcin. *Statistical analysis:* Kuppermann and Glaser. *Obtained funding:* Glaser. *Administrative, technical, and material support:* Park and Glatter. *Study supervision:* Kuppermann, Marcin, and Glaser.

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### Announcement

**Submissions.** The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: <http://archpedi.ama-assn.org>.