JPPT | Retrospective Clinical Investigation

Impact of Body Habitus on the Outcomes of Pediatric Patients With Diabetic Ketoacidosis

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OBJECTIVE To determine whether obese and overweight pediatric patients with new onset diabetic ketoacidosis (DKA) treated with continuous infusion insulin have increased time to subcutaneous insulin initiation or adverse events as compared with patients with normal body habitus.

METHODS A retrospective, cohort study was designed that included patients 2 to 18 years of age admitted with new onset DKA who received continuous infusion insulin from January 1, 2011, to December 31, 2017. Patients were stratified according to BMI percentile with the primary outcome of time to initiation of subcutaneous insulin. Secondary endpoints included time to minimum beta-hydroxybutyrate, and incidence of hypoglycemia or other adverse events.

RESULTS A total of 337 patients (46.6% male, 9.6 ± 3.8 years of age) met study criteria. Patients were classified by body habitus as obese (7.7%, n = 26), overweight (7.1%, n = 24), normal body weight (58.8%, n = 198), or underweight (26.4%, n = 89), based on BMI percentile. Most patients were initiated on insulin at 0.1 unit/kg/hr (86.7%) for 16.7 ± 7.0 hours. Time from continuous infusion insulin initiation to subcutaneous insulin was not different between body habitus groups, nor was hypoglycemia or the use of mannitol ($p > 0.05$). Median time to lowest beta-hydroxybutyrate was greater for obese (26.4, IQR [13.9, 41.9]) and overweight (32.4, IQR [18.3, 47.0]) groups than for normal body habitus patients (16.5, IQR [12.3, 23.8]) ($p < 0.05$).

CONCLUSIONS Time to subcutaneous insulin and adverse events was not associated with body habitus, but obese and overweight patients may have delayed beta-hydroxybutyrate clearance.

ABBREVIATIONS BHB, beta-hydroxybutyrate; BMI, body mass index; CDC, Centers for Disease Control and Prevention; DKA, diabetic ketoacidosis

KEYWORDS body mass index; diabetic ketoacidosis; insulin; obesity; pediatrics

J Pediatr Pharmacol Ther 2021;26(2):194–199

DOI: 10.5863/1551-6776-26.2.194

Introduction

Pediatric patients with diabetic ketoacidosis (DKA) are commonly encountered in emergency centers around the country, and much literature has been published regarding improving the quality of care for these patients.[1–6] It is common teaching that pediatric patients with DKA typically present with a BMI in the lower percentiles for age and sex and most providers have experience in treating this population. As the prevalence of pediatric obesity has increased in the United States over the past few decades, pediatric patients who are overweight or obese are now presenting to emergency departments with DKA.[7–9] The obese and overweight pediatric population with DKA represents a new subgroup of patients encountered more frequently. One of the concerns with the treatment of the obese and overweight pediatric patient is using weight-based dosing of medications.

Prior publications have noted significant differences in dosing methodologies for obese pediatric patients as compared with normal-weight pediatric patients. For example, aminoglycosides, a class of highly water-soluble antibiotics, require dosing adjustment for obese and overweight patients.[10] Dosing of continuous infusion insulin is weight based (units/kg/hr) and excess insulin dosing, due to a high percentage of adipose tissue, could result in adverse events such as hypoglycemia, or could potentially result in increased dose titrations and increased length of therapy. Alternatively, obese patients may have a degree of insulin resistance, which would necessitate the use of higher doses of insulin to reverse ketosis in a timely manner.[7] To improve the care of pediatric DKA patients, it is necessary to evaluate the effect that BMI has on the outcomes of pediatric patients with DKA treated with a continuous infusion of insulin. Obese and overweight pediatric patients with DKA treated with continuous infusion insulin may have differences in resolution of DKA as compared with patients with normal body habitus.

Materials and Methods

A retrospective, cohort study was designed and institutional review board approval was obtained through Baylor College of Medicine and affiliated institutions. The electronic medical record at Texas Children's

Table 1. Baseline Variables Categorized by Body Habitus

Category	Obese (n = 26)	Overweight (n = 24)	Normal (n = 198)	Underweight (n = 89)
Male, %	65.4	50.0	45.5	42.7
Hispanic, %	57.7*	58.3*	28.4	30.1
Age, mean ± SD, yr	10.3 ± 2.9	10.4 ± 3.7	9.7 ± 3.7	9.0 ± 4.2
BMI, kg/m^2	26.2 ± 5.8*	21.9 ± 3.1*	16.7 ± 2.1	13.5 ± 1.2*
BMI percentile	97.2 ± 1.5*	91.5 ± 2.7*	39.1 ± 25.1	1.3 ± 1.6*
Baseline laboratory values				
pH	7.11 ± 0.11	7.07 ± 0.15	7.11 ± 0.12	7.12 ± 0.12
Bicarbonate, mEq/mL	8.5 ± 2.9	7.7 ± 3.2	8.0 ± 2.9	8.5 ± 3.0
BHB, mg/dL	8.2 ± 2.5	8.2 ± 2.2	8.6 ± 2.2	8.4 ± 2.2
Blood glucose, mg/dL	415 ± 160	410 ± 164	417 ± 162	455 ± 149
Initial insulin dose, %, units/kg/hr				
0.01	0	0	0	1.1
0.05	3.9	8.3	11.6	20.2
0.1	96.2	91.7	88.4	78.8

BHB, beta-hydroxybutyrate
* $p < 0.05$ as compared with normal body habitus patients.

Hospital was queried for inpatients who had received continuous infusion insulin and had a positive result for insulin antibodies (GAD, ICA512, insulin antibody) from January 1, 2011, to December 31, 2017.

Patients were included in the study if they were 2 to 18 years of age, were diagnosed with DKA (as defined by the presence of insulin antibodies, a pH of <7.30 on admission, and a bicarbonate value of <15 mEq/mL on admission), and were initiated on a fluid protocol ("two-bag method") and continuous infusion of regular insulin for treatment of DKA in one of the emergency centers in our health system. Dosing of continuous infusion insulin was left to the discretion of the provider and the two-bag method was a standard for fluid management for patients with DKA at our institution for the entire study period (Supplemental Table S). Patients were excluded from the dataset if they had received insulin prior to admission to our emergency center, had undergone cardiopulmonary resuscitation prior to or during the admission, were intubated or mechanically ventilated, or had a surgical procedure during the admission. If the patient was admitted multiple times during the review period, only the first admission was used.

Data collection included patient age, sex, height, weight, admission/discharge date and time, continuous infusion insulin starting dose, increases or decreases in the continuous infusion dose, and length of continuous infusion insulin. The following laboratory variables were collected prior to initiation of continuous infusion insulin therapy: blood glucose (mg/dL), pH, beta-hydroxybutyrate (BHB) (a ketone) (mg/dL), and bicarbonate (mEq/L). Time endpoints collected were based from initiation of continuous infusion insulin and included time of initiation of subcutaneous insulin, time to lowest BHB, and time to first bicarbonate value ≥15 mEq/L. Minimum blood glucose value during continuous infusion insulin was captured and the use of mannitol for increased intracranial pressure or dextrose for hypoglycemia was also reported.

Laboratory values above or below the detectability of the test were considered to be the maximum or minimum value of the test as appropriate for analysis (e.g., a blood glucose value reported as >500 mg/dL was considered to be 500 mg/dL for purposes of analysis). Hypoglycemia was defined as a blood glucose <70 mg/dL while receiving continuous infusion insulin therapy.

The primary endpoint was time from initiation of insulin continuous infusion to administration of subcutaneous insulin. Secondary endpoints included time from insulin infusion initiation to lowest BHB, time from insulin continuous infusion initiation to bicarbonate ≥15 mEq/mL, use of mannitol, percentage of patients with continuous infusion insulin dose titrations, incidence of hypoglycemia, and hospital length of stay. All endpoints consisted of comparison of obese, overweight, and underweight patients to patients with normal body habitus.

Descriptive statistical methods were used (mean ± SD, median, IQR, and percentage) to characterize the population. Patients were stratified by BMI percentiles into obese (BMI >95th percentile for age and sex), overweight (85th–94th percentile), normal (5th-84th percentile), and underweight (<5th percentile) per CDC guidelines.[8] Analysis of variance, chi-square analysis, and the Kruskal-Wallis test were used, based upon normality of the data, to determine if differences between group variables were statistically significant with normal

Table 2. Endpoints and Adverse Events Categorized by Body Habitus

Category	Obese (n = 26)	Overweight (n = 24)	Normal (n = 198)	Underweight (n = 89)
Hospital length of stay, median (IQR), days	3.1 (2.7, 4.4)	3.1 (2.4, 4.0)	3.1 (2.3, 3.9)	3.1 (2.4, 3.7)
Time endpoints				
Time to subcutaneous insulin, median (IQR), hr	15.7 (10.9, 21.1)	16.7 (13.4, 24.4)	15.2 (12.0, 19.3)	15.5 (11.2, 18.9)
Lowest BHB, mean ± SD, mg/dL	0.83 ± 0.49	0.63 ± 0.41	0.65 ± 0.40	0.51 ± 0.38*
Time to lowest BHB, median, (IQR), hr	26.4 (13.9, 41.9)*	32.4 (18.3, 47.0)*	16.5 (12.3, 23.8)	16.1 (12.8, 28.0)
Time to bicarbonate ≥15 mEq/L, median (IQR), hr	9.6 (7.2, 13.6)	12.5 (8.9, 18.7)	10.0 (6.5, 13.6)	8.1 (6.0, 11.9)*
Insulin therapy				
Length of insulin infusion, median (IQR), hr	15.1 (10.5, 21.8)	16.8 (12.7, 25.4)	15.6 (12.6, 19.6)	15.9 (12.6, 19.8)
Minimum dose, mean ± SD, units/kg/hr	0.08 ± 0.04	0.08 ± 0.04	0.08 ± 0.03	0.08 ± 0.04
Maximum dose, mean ± SD, units/kg/hr	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.02	0.09 ± 0.02
Changes in continuous infusion insulin dose, %				
Decrease in dose titration	26.9	20.8	24.2	17.9
Increase in dose titration	11.5	12.5	10.1	11.2
Adverse events				
Hypoglycemia, %	7.7	16.7	23.2	15.7
Number of hypoglycemic values, median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Lowest blood glucose during admission, mean ± SD, mg/dL	59 ± 9	59 ± 11	58 ± 11	56 ± 12
Lowest blood glucose during infusion, mean ± SD, mg/dL	123 ± 46	119 ± 38	110 ± 41	130 ± 51*
Treatment of hypoglycemia				
Dextrose, %	0.0	4.2	1.0	1.0
Mannitol, %	3.9	4.2	1.0	2.3

BHB, beta-hydroxybutyrate

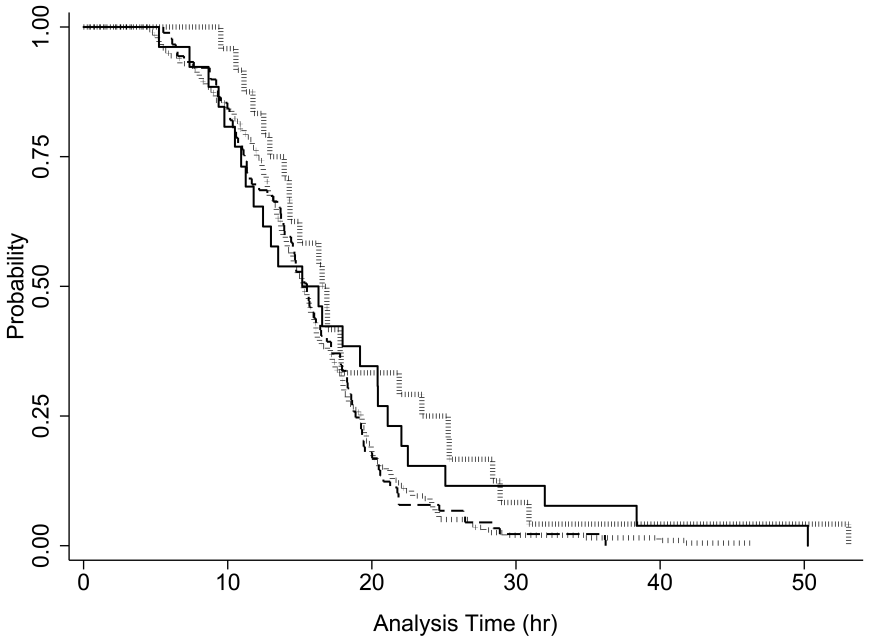
* $p < 0.05$ as compared with normal body habitus patients.

body habitus patients as the referent group. Kaplan-Meier analysis with log-rank test was used to graphically evaluate the primary endpoint of time from initiation of continuous infusion insulin to initiation of subcutaneous insulin. Kaplan-Meier analyses were used to determine differences in the secondary endpoints of length of stay, time to lowest BHB, and time to bicarbonate ≥15 mEq/mL. All data analysis was performed with Excel 2013 (Microsoft, Redmond, WA) and Stata IC version 12 (StataCorp, College Station, TX). A p value of <0.05 was considered statistically significant *a priori*.

Results

Initially, 1880 patients admitted who received a continuous infusion of insulin underwent review, and 664 were initially admitted for DKA. After further review, patients were excluded primarily for receipt of insulin prior to admission, and a total of 337 patients met study criteria (46.6% male, mean age of 9.6 ± 3.8 years, 32.3% (n = 109) Hispanic ethnicity). Mean BMI was 16.9 ± 4.2 kg/m^2 and body habitus was categorized as follows: obese (7.7%, n = 26), overweight (7.1%, n = 24), normal body weight (58.8%, n = 198), underweight (26.4%, n = 89). Median length of stay was 3.1 days (IQR, 2.3, 6.1) for the study cohort. Baseline laboratory values, prior to initiation of insulin, were as follows: blood glucose 426 ± 159 mg/dL, pH 7.11 ± 0.12, BHB 8.5 ± 2.2 mg/dL, bicarbonate 8 ± 3 mEq/L.

Figure 1. Time to subcutaneous insulin after initiation of continuous infusion insulin stratified by body habitus.



| | | | Normal; — Obese; |||||| Overweight; – – – Underweight

Patients were initiated on a dose of insulin at 0.1 unit/kg/hr (86.7%), 0.05 unit/kg/hr (13.1%), or 0.01 unit/kg/hr (0.3%) at a mean of 2.4 ± 1.1 hours after admission to the emergency department. Patients received continuous infusion insulin for 16.7 ± 7.0 hours. Overall, 22.6% (n = 76) of patients had a decrease in insulin infusion dose and 10.7% (n = 36) required an increase in insulin infusion dose during therapy. As body habitus increased, there was a trend to use higher (0.1 unit/kg/hr) starting dose for insulin infusion, but with no differences in incidence of increasing or decreasing dose titration (Tables 1 and 2).

Patients were initiated on subcutaneous insulin at 16.2 ± 6.9 hours after initiation of continuous infusion insulin. Time to achieving minimum BHB was 24.3 ± 18.1 hours and time to bicarbonate ≥15 mEq/L was 16.6 ± 1.6 hours after initiation of continuous infusion insulin. The mean minimum blood glucose value for patients during the insulin infusion was 117 ± 44 mg/dL; hypoglycemia occurred in 19.6% (n = 66) of patients, and 1.2% (n = 4) required a dextrose bolus for hypoglycemia. Mannitol, for treatment of cerebral edema, was required in 1.8% (n = 6).

When categorized by body habitus, the only significant difference in baseline characteristics was the increased percentage of Hispanic ethnicity in the overweight and obese groups, as compared with the normal body habitus group ($p < 0.05$) (Table 1). No statistically significant differences were noted in the primary endpoint of time from continuous infusion insulin initiation to subcutaneous insulin initiation between groups. Underweight patients had a higher mean minimum blood glucose value during continuous infusion and lower final BHB value on univariable analysis, and patients in the obese and overweight groups had a significantly longer time to minimum BHB than the normal body habitus group ($p < 0.05$) (Table 2).

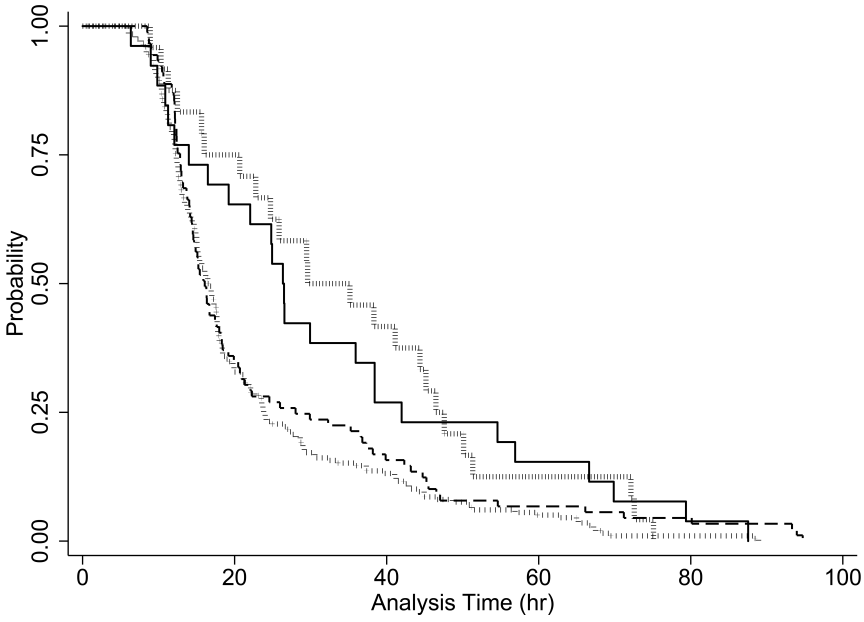
Kaplan-Meier analysis with log-rank test for time to subcutaneous insulin did not identify any statistically significant differences between BMI categorizations ($p = 0.08$) (Figure 1). Subsequent analyses identified significant differences in time to BHB in obese and overweight patients as compared with patients with normal body habitus ($p < 0.05$) (Figure 2).

Discussion

This is the first evaluation of outcomes in pediatric DKA patients treated with continuous infusion insulin based upon body habitus. Few differences were noted between body habitus groups, suggesting that the current standard of therapy for continuous infusion of insulin in the treatment of DKA is appropriate for any body habitus grouping.

We found no difference in the primary outcome of time to subcutaneous insulin initiation between each of the 4 groups, demonstrating that BMI does not have an effect on outcomes that we measured in pediatric DKA patients treated with continuous insulin infusion. From these data, we do not recommend alterations in continuous infusion insulin dose in obese or overweight pediatric patients with DKA. We noted that in the underweight patient population, there was a trend

Figure 2. Time to lowest beta-hydroxybutyrate concentration after initiation of continuous infusion insulin stratified by body habitus.



| | | | Normal; — Obese; |||||| Overweight; – – – Underweight

toward using lower initial doses of continuous infusion insulin. While the focus of our investigation was dosing in the overweight patient, the alteration of doses of continuous infusion insulin in any group, based on body habitus, does not appear to be necessary.

Interestingly, we noted that patients in the obese and overweight groups had a longer time to clearance of BHB than patients with normal body habitus. Data in adults show that BHB clearance is reduced in patients with obesity.[11] This may be a spurious finding and does not appear to have contributed to the overall outcomes of DKA patients at our institution. However, this can be useful information for providers caring for this patient population when interpreting laboratory values and developing plans for medical management.

The limitations associated with retrospective evaluations are present in this investigation, and the results should be interpreted in light of the study design. The fluid management was standard at our institution (the two-bag method) and we have made the assumption that there was little deviation from the protocol. We cannot comment on the impact of fluid management in DKA for the obese and overweight groups because we did not collect total intake and output values. We chose a patient group that was relatively homogeneous: first admission for DKA, no prior exposure to insulin therapy, and no significant comorbidities such as cardiopulmonary resuscitation, surgical procedures, or mechanical ventilation. It is possible that we have selected a particularly "healthy" group of patients for this analysis. Therefore, we cannot comment on the management of pediatric patients with type I diabetes and DKA outside of the patient population we have selected. Further evaluation of the obese pediatric patients with type I diabetes would be necessary, as this patient population would likely represent a very challenging subgroup to manage.[7]

Conclusions

Time to subcutaneous insulin and adverse events was not associated with body habitus in pediatric inpatients with DKA on continuous infusion insulin. Obese and overweight patients with DKA may have delayed clearance of beta-hydroxybutyrate.

Article Information

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. BSM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. The project was approved by the Baylor College of Medicine Institutional Review Board, but was exempt from informed consent.

Submitted. February 4, 2020

Accepted. June 6, 2020

Supplemental Material. DOI: 10.5863/1551-6776-26.2.194.S

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