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Cortisol Levels in Children With Diabetic Ketoacidosis Associated With New-Onset Type 1 Diabetes Mellitus: A Retrospective Review

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Abstract

There is little data documenting cortisol levels in children with diabetic ketoacidosis (DKA), despite the fact that untreated adrenal insufficiency (AI) could worsen the outcome of DKA. In this cross-sectional study, we assessed serum cortisol levels in 28 children with DKA and new onset type 1 diabetes mellitus evaluated at our center over a 5-year period. Average duration of diabetes-related symptoms was positively associated with age ($P = .002$), and significantly lower hemoglobin A1c levels were observed in the youngest children. The mean cortisol level was 40.9 mg/dL, with a range of 7.8 to 119 mg/dL. Cortisol levels were found to be inversely associated with serum pH ($P = .007$). There was no difference in the clinical outcome of the 4 patients who had cortisol levels less than 18 mg/dL. Overall, we did not find clinical or laboratory evidence of diminished cortisol reserve; however, the possibility of AI must be kept in mind when treating children with DKA.

Keywords

type 1 diabetes mellitus; adrenal insufficiency; diabetic ketoacidosis; cortisol; autoimmune

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Author Contributions

KMW drafted the article and revised it critically for important intellectual content, made a substantial contribution to the concept and design, acquisition of data and analysis and interpretation of data, and approved the final version to be published. PF made a substantial contribution to the concept and design, acquisition of data or analysis and interpretation of data, and approved the final version to be published. SEO revised the draft critically for important intellectual content, made a substantial contribution to the concept and design, acquisition of data and analysis and interpretation of data, and approved the final version to be published. MPG made a substantial contribution to the concept and design, acquisition of data or analysis and interpretation of data, and approved the final version to be published. GA made a substantial contribution to the concept and design, acquisition of data or analysis and interpretation of data, and approved the final version to be published.

Declaration of Conflicting Interests

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Introduction

The association between type 1 diabetes mellitus (T1DM) and other autoimmune diseases is well known. As such, screening of patients with T1DM for disorders such as celiac and thyroid disease has become commonplace in routine diabetes-related patient care.^{1,2} Addison's disease (AD), the most common cause of primary adrenal insufficiency (AI),³ occurs with increased frequency in patients with T1DM.⁴ Adrenal cortex antibodies and 21-hydroxylase antibodies are present in as many as 90% of patients with AD.^{3,5} The estimated prevalence of coexisting adrenal autoantibodies and T1DM is 0.5% to 3%,^{6–9} with risk of progression to clinical disease of 14% to 40% per year, based on reports of varied sample size.^{3–5,10}

Nevertheless, screening for AD in children with T1DM remains controversial because the diagnosis of diabetes usually precedes the onset of AD by many years.^{6,11} There are few reports of patients with T1DM who developed AD in childhood.^{12,13} Almost all these patients were known diabetics who presented with symptoms of AI. Furthermore, there is little documentation of the adequacy of adrenal reserve in this pediatric population. More than half the children diagnosed with T1DM may present with diabetic ketoacidosis (DKA) at the time of diagnosis.^{14–16} This acute hyperglycemic state has been associated with an elevation of proinflammatory markers, oxidative stress,^{17–19} and risk for significant morbidity and mortality.²⁰ Nonetheless, evaluating cortisol levels during the stress of DKA may provide additional information about the integrity of a patient's adrenal reserve in this presumed at-risk population.

Elevated cortisol secretion rates have been documented in patients with diabetes and DKA; however, most studies include patients with known diabetes.^{21,22} There are reports of increased frequency of AI in critically ill children and adults as assessed by Adrenocorticotrophic Hormone (ACTH) stimulation testing.^{23–26} None of these studies specifically addressed patients with diabetes and DKA. As stimulation testing is not practical at the time of presentation and treatment of children with newly diagnosed T1DM, we sought to determine the adequacy of their serum cortisol response to the stress of DKA by retrospective review.

Methods

Participants

Hospital records of pediatric patients with DM presenting to the emergency department at New York Presbyterian Columbia University Medical Center during the years 2009–2013 were retrospectively reviewed. Patients who were identified as having new-onset T1DM and presenting with DKA were included. DKA was defined by blood glucose levels greater than 200 mg/dL, pH <7.30, serum bicarbonate levels <15 mmol/L, and the presence of ketones.²⁷ The study was approved by the Columbia University Institutional Review Board, and a waiver of informed consent was obtained.

Sex, age, anthropometric data, initial vital signs on arrival to the emergency department, and reported diabetes-related symptoms recorded in the initial intake were obtained from

hospital records for analysis. Biochemical assessment included the following laboratory specimens obtained at the time of presentation prior to initiation of insulin therapy: hemoglobin A1c, insulin, c-peptide, venous blood gas, basic metabolic panel for electrolytes and renal function, urine ketones, thyroid function tests, and serum cortisol levels. The autoimmune status of patients was assessed by collection of glutamic acid decarboxylase-65 antibodies, insulin autoantibodies, and islet-cell autoantibodies as well as antithyroid peroxidase and antithyroglobulin antibodies, tissue transglutaminase IgA, and total IgA. Resolution of DKA was defined by pH >7.35 or serum bicarbonate levels >15 mmol/L.

Assays

Serum cortisol levels were determined at the NYPH Columbia University Medical Center Laboratory (New York, NY) via chemiluminescent immunoassay. Of 27 islet cell autoantibodies, 23 were analyzed by semi-quantitative indirect fluorescence at ARUP laboratories (Salt Lake City, UT) and the remainder by immunoprecipitation at Esoterix. Insulin autoantibodies were analyzed at ARUP by quantitative radioimmunoassay (22/25) and by insulin-I125 binding at Esoterix. GAD65 antibodies were analyzed at 3 sites: by quantitative enzyme-linked immunosorbent assay at ARUP (13/25), by immunoprecipitation assay at Esoterix (7/25), and by radioimmunoassay at Mayo Medical Laboratories (Rochester, MN; 5/25). The presence or absence of antibodies was recorded irrespective of titer or methodology used.

Statistical Analysis

Statistical analyses were performed using SAS software (9.3, SAS Institute Inc, Cary, NC). Continuous data are reported as mean $\pm$ SDs. Categorical data are reported as numbers and percentages. Differences among groups were analyzed via general linear models. For nonparametric data, the Kruskal-Wallis test was used. Pearson's correlation was used to assess relationships between cortisol levels and other analytes. Spearman's rank-order correlation was used for nonnormally distributed variables. A *P* value of <.05 was used for level of significance.

Results

A total of 113 children and adolescents were identified as having new-onset T1DM at presentation to our emergency department over a 5-year period. This number does not include the larger group of patients who did not require inpatient management and were referred initially to our outpatient diabetes center. Of these patients, 60 were found to be in DKA on presentation to our institution; 14 patients were excluded because initial laboratory evaluation was performed at an outside hospital or blood work obtained as part of our protocol was collected after insulin and rehydration was initiated. Furthermore, 18 patients did not have either T1DM-related autoantibodies or cortisol levels for analysis in our laboratory. Therefore, 28 patient records met criteria for review in this study. No patients were known to have thyroid, adrenal, or other endocrine disorders at the time of presentation.

Clinical characteristics are summarized in Table 1. Of the 28 children and adolescents, there were 11 male and 17 female patients. Data were divided by age into 3 groups. Group 1 consisted of patients of 0 to 5 years old ($n = 8$); group 2, 6 to 10 years old ($n = 11$); and group 3, 11 to 15 years old ($n = 9$). The mean age was 8.6 ± 4.5 years, with a range of 16 months to 15.5 years. All patients were positive for at least 1 T1DM-related autoantibody, with the majority testing positive for at least 2 autoantibodies. Thyroid antibodies (antithyroid peroxidase or antithyroglobulin antibodies) were available for review in 17 children, and 4 of the 17 (23.5%) were positive for at least 1 antibody. No patient had a positive celiac screen by tissue transglutaminase IgA antibody testing.

The average duration of diabetes-related symptoms (polyuria, polydipsia, weight loss) prior to presentation in all patients was 2.4 ± 2.2 weeks (Table 2) and was found to be positively associated with age ($r = 0.58$; $P = .002$) and weight ($r = 0.60$; $P = .0009$). At time of diagnosis, mean hemoglobin A1c levels were 12.53 ± 2.05 % and differed significantly among all groups ($P = .008$). We found that lower A1c levels were observed in group 1 compared to groups 2 and to group 3 ($P = .009$ and $P = .004$, respectively), but not between groups 2 and 3 ($P = .63$).

Initial pH and bicarbonate levels also varied across age groups ($P = .025$ and $P = .03$, respectively); however, there was no significant difference in length of time until resolution of DKA between groups. The mean and median serum cortisol responses were 40.9 and 37.5 mg/dL, respectively, with a range of 7.8 to 119 mg/dL among all children. Average levels were greatest in group 2 but did not reach statistical significance ($P = .077$). Serum cortisol levels were found to be inversely associated with serum pH ($r = -0.48$; $P = .007$) and serum bicarbonate results ($r = -0.40$; $P = .036$).

On presentation with DKA, there were 4 patients (Table 3) who had cortisol levels less than 18 mg/dL, which by convention has been used as the lowest peak response suggestive of intact adrenal function in response to ACTH stimulation testing.^{23,24,26} There was no statistical difference in initial pH, initial bicarbonate levels, or period of time until resolution of DKA compared with the rest of the cohort, nor did these patients have less optimal outcomes at the time of hospital discharge.

Discussion

To our knowledge, this is the first study to assess the cortisol response to the stress of DKA in a large cohort of pediatric patients with new-onset T1DM. The incidence of T1DM has steadily increased over recent years.^{28,29} Whereas the prevalence of concomitant AD is lower compared with other associated autoimmune disorders^{3,8} associated with T1DM, the risk of undiagnosed AI in this growing population of pediatric patients has not been fully described. At this time, there is no consensus for the screening of AD in patients with diabetes as compared with the currently accepted guidelines for other autoimmune disease associated with diabetes.^{1,6,8,11,12} Some authors propose screening patients for clinical signs of AI prior to undertaking a laboratory investigation of adrenal function.¹¹ However, symptoms of AI are generally nonspecific and may easily be missed, especially in the setting of another known cause of acute illness. In addition, subclinical stages of AD as

characterized by the varied responses to ACTH stimulation testing may precede clinical disease by many years.^{4,5,30} Patients with autoimmune AI who are asymptomatic may have a loss of adrenal responsiveness to ACTH as evidenced by a decreased peak cortisol response.^{5,31,32} In patients with mild hypocortisolism, this finding of progressive decline in adrenal function may also be missed with standard-dose ACTH testing.^{26,32}

More than half of the patients evaluated in our inpatient center presented with DKA at the time of diagnosis. This is higher than the estimated 25% of patients with new-onset T1DM reported in US populations,¹⁶ likely a result of increasing referrals to our outpatient center at the time of presentation. Nevertheless, this allowed us the opportunity to evaluate cortisol levels as a marker of adrenal reserve, even without the measure of adrenal autoantibodies, in an at-risk population during a known physiological stressor.^{18,19,33} As shown in the above results, mean cortisol levels for all 3 age groups were elevated. Patients were divided by age because the prevalence of AD is found to be higher in older patients⁴; however, we did not find a statistical difference in cortisol response by age. Cortisol levels were positively associated with the degree of acidosis at the time of diagnosis. They were not found to be positively or negatively associated with the duration of symptoms prior to presentation or with the length of time until resolution of DKA.

Annane et al³⁴ have raised concerns that higher basal cortisol levels, as defined by a level greater than 34 mg/dL, in adult patients who are ill may also be predictive of increased mortality risk. More than half of the patients in our study presented with cortisol levels greater than 34 mg/dL, and 1 patient had a level of 119 mg/dL. As discussed before, none of our patients experienced any complications during DKA treatment. Most were able to be transitioned to subcutaneous insulin within 2 to 3 days, and all were subsequently discharged home.

We found that, on average, younger children were diagnosed after a shorter period of diabetes-related symptoms (polyuria, polydipsia, and weight loss) and had lower hemoglobin A1c levels at the time of diagnosis. This is in accordance with other reports of children with new-onset T1DM^{35–37} and is possibly because of closer supervision by caretakers of younger children. Though we might have expected the older children, who were symptomatic, on average, for almost a month prior to presenting in DKA, to have a more significant degree of acidosis and higher cortisol levels than the younger children, they did not. These older children actually had higher serum bicarbonate levels at presentation, and their cortisol levels were not significantly different from those of the other children. There was a trend toward shorter time to resolution of DKA with increased age; however, this was not found to be significant. The ability of the older child to better compensate for the metabolic changes accompanying the decline in insulin production may account for these findings.

Evaluation of the adrenal response can be performed via various tests and is further complicated by controversy regarding optimal dose of ACTH in stimulation testing and cutoff levels used to define AI.^{25,26} We chose 18 mg/dL as the cutoff for the lower level of acceptable adrenal response because this has been more consistently applied in past studies. In the 4 patients with cortisol levels less than this level, there was no association with age at

diagnosis. None of the 4 met criteria for severe DKA at presentation, and 3 patients were classified as having mild DKA (pH >7.20).³⁸ Furthermore, this subset of patients was not found to have significantly abnormal vital signs at presentation. Hypercortisolism, as a response to illness and stress, helps regulate vascular tone, myocardial function, and the immune response.²⁶ Biochemical evidence of AI has been observed in 17% to 90% of critically ill pediatric patients at the time of illness in some reports.^{23–25,39} Widespread variation in incidence of AI is likely a result of lack of consensus in diagnostic criteria, inconsistent testing methods, and variability in severity of illness.⁴⁰ Despite this, the presence of hemodynamic instability, including persistent tachycardia and fluid-refractory hypotension, appears to be a consistent finding in patients with AI associated with critical illness.^{25,39–42} Mild disturbances in vital signs in our patients may represent the dehydration accompanying DKA at initial presentation because none of the 4 patients with lower cortisol levels in this review had persistent hypotension nor required treatment outside of routine care. Available records for these patients followed 1 to 3 years after diagnosis do not report any persistent episodes of hypoglycemia or other signs of glucocorticoid deficiency.

Limitations in this study include lack of comparison cortisol levels in patients with new-onset T1DM without DKA. The retrospective nature of this study may have led to a decreased sample size for analysis and reporting bias among caretakers. Another limitation is a lack of ACTH levels that may have provided insight into the overall response of the hypothalamic-pituitary-adrenal axis. Furthermore, lack of measure of adrenal autoantibodies did not allow us to confirm the potential etiology of the low cortisol reserve and risk of AI in the patients highlighted above. We will attempt to follow these patients prospectively in the future.

Conclusion

Currently, there are no established clinical guidelines to evaluate the risk of AI in pediatric patients with T1DM. Based on the data reviewed in this study and reassuring outcomes in those patients with lower cortisol responses, we have not found sufficient evidence to recommend routine measurement of cortisol levels in all children with newly diagnosed T1DM presenting with DKA. Close clinical monitoring of these patients is still recommended because undiagnosed AI may lead to significant morbidity and mortality if left untreated.

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Table 1

Clinical Characteristics of Children With Newly Diagnosed T1DM in DKA (n=28).

	Total	Group 1 (0–5 years)	Group 2 (6–10 years)	Group 3 (11–15 years)
n (%)	28 (100%)	8 (29%)	11 (39%)	9 (32%)
Sex (M/F)	11 (39.3%)/17 (60.7%)	5 (62.5%)/3 (37.5%)	1 (9.1%)/10 (90.9%)	5 (55.6%)/4 (44.4%)
Age (years)	8.6 ± 4.5	2.8 ± 1.6	8.8 ± 1.5	13.4 ± 1.7
Weight (kg)	32.9 ± 18.4	14.2 ± 3.5	38.9 ± 18.9	42.6 ± 13.5
Autoimmune thyroid disease screen (positive), n = 17	4 (23.5%)	0 (0%)	2 (28.6%)	2 (40%)
Celiac screen (positive)	0	0	0	0

Abbreviations: T1DM, type 1 diabetes mellitus; DKA, diabetic ketoacidosis; M, male; F, female.

Table 2

Laboratory Evaluation at Time of Diagnosis.

	Total (n = 29)	Group 1 (0–5 years)	Group 2 (6–10 years)	Group 3 (11–15 years)	P
Duration of symptoms prior to presentation (weeks)	2.4 ± 2.2	1.2 ± 0.6	2.5 ± 2.7	3.4 ± 2.2	.05
HbA1c (%)	12.53 ± 2.05	10.75 ± 1.77	13.07 ± 1.59	13.46 ± 1.93	.008
Initial blood glucose (mg/dL)	535.43 ± 138.03	507.38 ± 89.46	554.64 ± 126.25	548.11 ± 196.91	.775
Initial pH	7.18 ± 0.08	7.21 ± 0.06	7.13 ± 0.10	7.21 ± 0.05	.025
Bicarbonate (mmol/L)	8.71 ± 4.45	7.75 ± 4.46	7.09 ± 3.99	11.56 ± 4.00	.034
Cortisol (mg/dL)	40.93 ± 25.39	26.76 ± 14.15	52.94 ± 29.9	38.84 ± 21.88	.077
Time until resolution of ketoacidosis (hours)	11.89 ± 10.15	11.25 ± 5.60	16.36 ± 13.28	7.00 ± 6.73	.117

Abbreviation: HbA1c, hemoglobin A1c.

Table 3
Characteristics of Children With Cortisol Levels <18 mg/dL at the Time of Diagnosis of New-Onset T1DM With DKA.

Patient ID Number	Age (years)	A1c (%)	Initial pH	Initial Glucose (mg/dL)	Serum Cortisol (mg/dL)
16	5.8	10.7	7.16	516	9.6
22	15.6	12.7	7.23	500	13.6
27	13.9	13.8	7.26	274	7.8
45	10.75	13.2	7.26	496	17.6

Abbreviations: T1DM, type 1 diabetes mellitus; DKA, diabetic ketoacidosis; A1c, hemoglobin A1c.