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Nonsevere Diabetic Ketoacidosis and Adrenal Insufficiency: Exploring the Impact of Glucocorticoid Replacement on Metabolic Outcomes and ICU Length of Stay

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Background: There is a paucity of clinical data on corticosteroid replacement in patients with adrenal insufficiency who present with nonsevere noncomplicated diabetic ketoacidosis.

Case Summary: We analyzed five consecutive admissions for diabetic ketoacidosis of mild/moderate severity due to insulin omission in a 21-year-old man with type 1 diabetes and stable Addison disease. Despite similar presentations, the approach to steroid replacement differed: maintenance/moderate doses of hydrocortisone (< 60 mg/d) or high stress-doses (≥ 120 mg/d). Resolution of diabetic ketoacidosis and ICU and hospital length of stay were prolonged when high-dose versus maintenance/moderate glucocorticoids were provided: 45.5, 47.0, and 63.0 versus 12.0, 24.5, and 31 hours, respectively.

Conclusions: Although our findings remain hypothesis-generating, our case study raises awareness on the importance of categorizing diabetic ketoacidosis by severity and complication status when deciding on the intensity of steroid replacement in patients with stable Addison disease. Excessive glucocorticoid administration may delay the resolution of nonsevere and otherwise noncomplicated diabetic ketoacidosis and prolong ICU and hospital stays.

Key Words: Addison disease; adrenal insufficiency; diabetic ketoacidosis; glucocorticoids; insulin omission; intensive care unit length of stay; resolution of ketoacidosis; stress-dose steroids; type 1 diabetes

Diabetic ketoacidosis (DKA), a potentially life-threatening complication of diabetes, is frequently managed in the ICU. Its presentation and outcomes greatly depend on the underlying precipitating factors and associated comorbidities (1, 2). Addison disease (AD), most commonly due to autoimmune disease, may coexist with type 1 diabetes (T1DM). DKA is a common cause of ICU admissions, and critical care physicians are likely to care for patients with DKA who also have AD. Currently, there is little guidance on how to manage steroid replacement in patients with DKA and AD other than the tenet of increasing glucocorticoid replacement in situations of stress.

We describe five sequential admissions for nonsevere DKA, all due to insulin omission, in a single patient with coexisting T1DM and stable AD. Glucocorticoid regimen was initiated with either maintenance/moderate stress-dose hydrocortisone (< 60 mg/d) or high stress-dose replacement (≥ 120 mg/d). We examined time to resolution of DKA, ICU, and hospital length of stay (LOS), as well as hypoglycemic and hypotensive events across admissions. Resolution of DKA was identified when the serum bicarbonate stabilized at greater than 15 mEq/L (15 mmol/L), anion gap was less than or equal to 10 and glucose was less than or equal to 200 mg/dL (11.1 mmol/L). Hypoglycemia was defined by a blood glucose less than or equal to 70 mg/dL (3.9 mmol/L) and clinically significant hypoglycemia if glucose less than 54 mg/dL (3 mmol/L). Time to resolution of DKA was determined from the time of initial blood chemistry documenting ketoacidosis to when chemistry showed resolution. ICU and hospital LOS were measured in hours from admission to departure time, and to and from

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the unit or hospital, respectively, using an "Admission, Discharge and Transfer Summary" tool in the electronic medical record. The University of Texas Medical Branch Institutional Review Board waived requirement for patient informed consent for publication of this work under protocol 14-450.

CASE PRESENTATION

A 21-year-old man with uncontrolled T1DM (hemoglobin A1C > 12% [108 mmol/mol]) was admitted to our teaching hospital five times over a 19-month period with DKA precipitated by insulin omission. He was diagnosed with T1DM at 11 years old and with AD as a 13-year old. His diabetes was managed with neutral protamine hagedorn and regular insulin, 15 units and 10 units twice a day, respectively. His living situation challenged insulin adherence, but he denied issues with insulin access. AD was stable on a regimen of hydrocortisone, 20 mg in the morning and 10 mg in the afternoon, and fludrocortisone 0.1 mg daily, to which he assured good compliance. Patient's body mass index was 18 kg/m^2 and his blood pressure (BP) at a routine clinic visit was 96/74 mm Hg.

Symptoms at presentation included nausea, vomiting, abdominal or chest pain, and, on one occasion, mild diarrhea. The patient consistently presented alert and oriented, hemodynamically stable, and afebrile, with no increased work of breathing. Serum glucose was less than or equal to 540 mg/dL (30 mmol/L) and bicarbonate 12–15 mmol/L (**Table 1**). Acute treatment involved IV fluids, electrolyte replacement, IV insulin, and antiemetics. Insulin therapy included a bolus of regular insulin, given at a variable dose of 0.1–0.175 units/kg (except once when self-administered immediately prior to admission), followed by insulin infusion at a rate of 0.1 units/kg/hr with hourly rate adjustments targeting a blood glucose reduction of 50–75 mg/dL per hour until reaching 200 mg/dL and maintaining

TABLE 1. Admissions for Diabetic Ketoacidosis Inpatient With Type 1 Diabetes and Addison's Disease

Clinical and Outcome Variables of Interest	High-Dose Glucocorticoids			Maintenance/Moderate Glucocorticoids			
	Admission 1	Admission 2	Group	Admission 3	Admission 4	Admission 5	Group
Findings on presentation							
Precipitating factor	Insulin omission	Insulin omission	Insulin omission	Insulin omission	Insulin omission	Insulin omission	Insulin omission
Mental status	Alert and oriented	Alert and oriented	Alert and oriented	Alert and oriented	Alert and oriented	Alert and oriented	Alert and oriented
Temperature (°C)	36.7	36.4	36.6	36.3	36.4	36.8	36.5
Blood pressure (mm Hg)	111/72	100/58	106/65	101/70	112/81	94/62	102/71
Heart rate (beats/min)	95	131	113	115	119	124	119
Respiratory rate (per min)	16	18	17	18	18	20	19
Oxygen saturation room air (%)	100	98	99	99	98	99	99
HbA1c (%) (mmol/mol)	13.6 (125)	14 (130)	13.8 (127)	14.4 (134)	> 14 (> 130)	12.6 (114)	> 13.5 (> 124)
Urine or serum ketones documented	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum bicarbonate (total CO2 mmol/L)	12	15	13.5	12	12	12	12
Anion gap	31	29	30	27	29	27	28
pH arterial or venous blood gas	7.35[a]	7.36[a]	7.4	7.23	7.28	7.26	7.26
Serum glucose (mg/dL) (mmol/L)	438 (24.3)	529 (29.3)	483.5 (26.8)	362 (20.1)	497 (27.6)	540 (30)	466 (25)
Corrected serum sodium (mmol/L)	141	136	138.5	131	138	134	134
Serum potassium (mmol/L)	5.6	4.6	5.1	5.2	5.8	5.4	5.5
Acute Physiology and Chronic Health Evaluation II score	2[a]	4[a]	3.0	5	7	6	6
Insulin regimen							
Initial bolus of regular insulin (units/kg)	0.15	0.1	0.13	n/a[b]	0.175	0.1	0.14
Initial infusion rate (units/kg/hr)	0.1	0.1	0.1	0.05[c]	0.1	0.1	0.08
Basal insulin for transition to subcutaneous (units/kg of glargine or equivalent)	0.15	0.22	0.19	0.18	0.18	0.2	0.19

(*Continued*)

TABLE 1. (*Continued*). Admissions for Diabetic Ketoacidosis Inpatient With Type 1 Diabetes and Addison's Disease

	High-Dose Glucocorticoids			Maintenance/Moderate Glucocorticoids			
	Admission 1	Admission 2	Group	Admission 3	Admission 4	Admission 5	Group
Steroid regimen							
Total hydrocortisone (mg/d)							
Day 1	120	150	135	20[d]	55[d]	30	35
Day 2	60	70	65	–	–	40[d]	40[d]
Day 3	20[d]	20[d]	20[d]	–	–	–	–
Time from arrival to first hydrocortisone dose (hr)	18	10	14 ± 5.7	15	13	17	15 ± 2.0
Fludrocortisone (mg/day)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Time from arrival to first fludrocortisone dose (hr)	18	61	39.5 ± 30.4	15	14	17	15 ± 1.5
Outcomes							
Clinically significant hypoglycemia events	0	0	0	0	0	0	0
Level 1 hypoglycemia events > 1 hr apart	1	1	1	0	1	1	0–1
Hypotensive events	0	0	0	0	0	1	0–1
Time to resolution of DKA (hr)	36	55	45.5 ± 13.4	16	13	7	12 ± 4.6
DKA relapse after transition to subcutaneous insulin	No	Yes	0–1	No	No	No	0
ICU length of stay (hr)	40	53	47 ± 9.2	Not applicable	33	16	24.5 ± 12.0
Hospital length of stay (hr)	67	59	63 ± 5.7	13	33	46	31 ± 16.6
Patient left against medical advice	Yes	Yes	Yes	No	No	No	No

DKA = diabetic ketoacidosis.
[a]Blood gas obtained 1–2 hr after initiating treatment with fluids and insulin; influences Acute Physiology and Chronic Health Evaluation Score calculation.
[b]Patient self-administered a subcutaneous bolus of 0.11 units/kg of regular insulin immediately prior to presentation.
[c]Patient treated with insulin infusion outside of ICU. Provider opted to use half of standard protocol rate.
[d]Administered dose of hydrocortisone until time of discharge.
Group shows descriptive summary, frequency, or mean ± SD.

below 200 mg/dL for transition to subcutaneous insulin (Table 1) (insulin rate 0.05 units/kg/hr on admission outside of ICU). Insulin infusion was transitioned to subcutaneous route using basal insulin at an average of ~0.2 units/kg and a total daily dose of 0.4 units/kg/d. There was great variability in steroid replacement on the first day: maintenance/moderate stress-dose hydrocortisone (20–55 mg) on three admissions and high-dose hydrocortisone (120 and 150 mg) on the remaining two (Table 1). There was no relationship between the choice of steroid replacement therapy, acidosis severity, or BP on presentation. Despite his history of AD, glucocorticoid replacement was delayed over 14 hours after arrival. On admission 5, steroids were given 17 hours after arrival and the patient developed hypotension requiring fluid boluses and additional hydrocortisone for stabilization (Table 1). There were no instances of clinically significant hypoglycemia. Mild hypoglycemia occurred on two admissions within each glucocorticoid replacement group.

Time to resolution of DKA was shorter when the patient received maintenance or moderate stress-dose hydrocortisone (mean ± SD) at 12.0 ± 4.6 hours than when high stress-doses were administered (45.5 ± 13.4 hr); likewise, with maintenance/moderate stress-dose hydrocortisone, mean ICU (24.5 ± 12 h) and hospital LOS (31.0 ± 16.6 h) were lower than that when high-dose steroids were administered (47.0 ± 9.2 hr and 63.0 ± 5.7 hr, respectively). The patient left against medical advice with unresolved hyperglycemia during his prolonged high stress-dose steroid admissions.

DISCUSSION

In patients with AD, steroid replacement needs to be increased during situations of stress. It is paramount that the severity of systemic compromise and degree of stress imposed by the hyperglycemic crisis be clearly defined when they present with DKA to provide appropriate glucocorticoid replacement. Guidelines recommend hydrocortisone up to 75 mg/d, in divided doses, with minor/moderate stress, and high doses of parenteral hydrocortisone (100-mg bolus, followed by doses of up to 200 mg/d) in situations of major stress, such as major surgery or trauma (3, 4). Fludrocortisone is not necessary in the setting of high stress-dose steroids (≥ 50 mg of hydrocortisone/d) (4).

DKA inhospital case fatality has decreased over time (5, 6), recently estimated at 0.4% (6). Furthermore, clinical severity scores and death rates in the ICU are lower in patients with DKA than in those without DKA. Freire et al (1) studied 584 patients admitted to an inner city ICU, 41 (7.4%) with DKA. Mean Acute Physiology and Chronic Health Evaluation (APACHE) II (12 ± 8), Logistic Organ Dysfunction System (2 ± 1), and Therapeutic Intervention Scoring System (21 ± 4) scores observed in patients with DKA were significantly lower than those without DKA (18 ± 10, 5 ± 4, and 28 ± 10.3, respectively). Importantly, there were no ICU deaths in the DKA group, whereas mortality reached 18% in patients without DKA (1). In another study, 76 patients admitted to the ICU with DKA were compared with age, sex, and APACHE II-matched non-DKA ICU patients. Although DKA patients had lower ICU mortality (4%) than their non-DKA matched controls (15%) (7), all DKA-related ICU deaths occurred in patients with severe DKA. Severe DKA, characterized by the presence of stupor or coma and severe anion gap metabolic acidosis (arterial pH of < 7.00) (2), correlated with a high Sequential Organ Failure Assessment Score and was more likely to result in vasopressor use, mechanical ventilation, and renal support (7). Work from several groups has helped define a group of patients with noncomplicated, nonsevere DKA deemed to be at low risk. These low-risk DKA adults include those under 65 years old who present without mental obtundation or coma, are not severely hypotensive or hypothermic, and do not have other medical conditions that merit ICU care (8). DKA admissions due only to insulin omission/noncompliance are associated with low disease severity scores, decreased ICU LOS, and low mortality (1).

During all DKA admissions, our young patient presented alert and oriented, afebrile and without multisystem compromise. Metabolic acidosis was of mild/moderate severity and hyperglycemia never reached the hyperosmolar range. Sodium and potassium serum levels were those typically seen in DKA (9). His AD was stable and well controlled. He had no associated acute precipitating illness; the only cause of DKA was insulin omission. His hyperglycemic crises were, by definition, noncomplicated and nonsevere, and associated with a low mortality risk (2, 10). Our patient was not in the ICU during one of his admissions, but he was treated with insulin infusion during all five hospitalizations. Insulin, fluid and electrolyte replacement, fludrocortisone, and maintenance or moderate dose increases in hydrocortisone restored the patient's baseline status on the three admissions in which this steroid approach was adopted, whereas recovery from DKA and ICU and hospital LOS appeared to be comparatively prolonged with high stress-dose steroids (Table 1). Increased glucocorticoid activity promotes hepatic and peripheral insulin resistance, increases counterregulatory hormones, and induces lipolysis and ketogenesis (11, 12), exacerbating the metabolic abnormalities already present in DKA. There are cases of DKA attributed to the use of high-dose steroids (13). In our patient, the metabolic burden of high-dose steroids may have contributed to the over three-fold increase in the time to resolution of DKA, when compared with lower dose steroid regimens, and by a difficult transition to subcutaneous insulin due to DKA relapse on one admission. However, it is important to recognize that our case study is limited by the small number of admission cases examined and by the inability to account for variability in insulin management and dietary factors before and during admission, among other confounders.

Each year about 6–8% of patients with known adrenal insufficiency have an adrenal crisis; patients with T1DM are at higher risk (4). Our patient's ability to mount a ketogenic response and develop ketoacidosis points to adequate outpatient glucocorticoid replacement (14, 15). However, a consistent delay in the initiation of steroid replacement was observed across hospital admissions. The patient did not receive corticosteroids until after a mean of 14.6 hours from arrival. In one admission, a 17-hour delay resulted in hypotension resistant to fluid replacement that responded well to moderate dose hydrocortisone and fludrocortisone. Prompt recognition of a patient's history of AD in the acute setting, such as through the use of personal alert bracelets/necklaces and electronic medical record flags, may avoid deleterious delays in glucocorticoid replacement and ensure that, if moderate steroid replacement is planned, fludrocortisone is included.

CONCLUSIONS

This case study contributes observational data from a small number of hospital admissions in a single patient. However, the literature is scarce with information on the management of DKA in patients with AD. The recurrent admissions differed mainly on the intensity of steroid replacement and offered a unique opportunity to question the definition of appropriate glucocorticoid replacement in patients with AD in the context of nonsevere noncomplicated DKA. It is important to emphasize that our observations remain hypothesis-generating; they are based on only five case admissions and are limited by confounding. Although specific glucocorticoid dosing recommendations cannot be made based on these exploratory observations, our findings raise awareness on the importance of categorizing DKA by severity and complication status when deciding on the intensity of steroid replacement in patients with coexisting and stable AD. Avoiding excessive steroid replacement may accelerate the resolution of DKA and reduce ICU and hospital stay. Current guidelines indicate increasing glucocorticoid replacement two-fold to three-fold in the setting of minor or moderate stress; our case series suggests that noncomplicated DKA of mild-to-moderate severity may fall in this category.

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