

Diabetic Ketoacidosis Associated With Cocaine Use

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Background: Multiple risk factors for diabetic ketoacidosis (DKA) have been described, including omission of insulin therapy and clinical conditions known to increase counterregulatory hormones. Recently, substance abuse has been identified in patients with DKA. We observed many cases of DKA in cocaine users, although the association between cocaine use and DKA has not been well described in the medical literature.

Methods: We performed a retrospective case-control study of admissions for DKA in cocaine users and non-user controls in an urban teaching hospital from January 1, 1985, to December 31, 1994.

Results: We identified 720 adult admissions for DKA. Twenty-seven cocaine users accounted for 102 admissions (14% of all DKA admissions). The users were compared with 85 nonuser controls who had 154 DKA admissions. Cocaine users had more admissions for DKA (mean, 3.78 vs 1.81;

$P = .03$). Cocaine users were less likely than controls to have an intercurrent illness identified as a precipitating factor for DKA (14.7% vs 33.1%; $P < .001$) and were more likely to have missed taking insulin prior to admission (45.1% vs 24.7%; $P < .001$). Although cocaine users had higher serum glucose levels on admission (32.9 mmol/L [593.4 mg/dL] vs 29.5 mmol/L [531.1 mg/dL]; $P = .03$), no differences in intensity of illness or treatment outcome were detected.

Conclusions: In this preliminary study, cocaine use was found in a significant number of adults admitted with DKA and was associated with more frequent omission of insulin therapy and the absence of precipitating systemic illness. Either because of its association with insulin therapy omission or its effects on counterregulatory hormones, cocaine use should be considered a risk factor for DKA, particularly in patients with multiple admissions.

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DIABETIC ketoacidosis (DKA) is a potentially fatal complication of diabetes mellitus characterized by hyperglycemia, the production of ketone bodies, and systemic acidosis.¹ Although traditionally attributed to absolute insulin deficiency, it is now believed that a relative insulin deficiency coupled with excess production of at least 1 counterregulatory hormone is required for excess hepatic ketoacid production.² Such counterregulatory hormones include catecholamines, cortisol, glucagon, and growth hormone.

A number of clinical conditions associated with increased production of these counterregulatory hormones are known to precipitate DKA, including infection,³ myocardial infarction,⁴ trauma,⁵ pheochromocytoma,⁶ Cushing disease,⁷ acromegaly,⁸ glucagonoma,⁹ and anaphylaxis.¹⁰ In addition, sympathomimetic agents such as terbutaline sulfate¹¹ have been reported to precipi-

tate DKA when used in patients with diabetes.

Cocaine has a potent effect on counterregulatory hormone concentrations. For example, in animal studies, cocaine increases catecholamine levels by stimulating the adrenal medulla to release epinephrine and norepinephrine.¹² Patients intoxicated with cocaine also have elevated norepinephrine and epinephrine levels.¹³ Other studies have found increased concentrations of corticotropin^{14,15} and cortisol^{16,17} in human subjects following cocaine administration. Thus, stimulation of either catecholamine release or the hypothalamic-pituitary-adrenal axis by cocaine use might act as a precipitating factor for DKA in patients with diabetes. Recently, Umpierrez et al¹⁸ reported cocaine use in 13% of adult patients admitted with DKA, and we have also observed multiple episodes of DKA among cocaine users admitted to our hospital. We conducted a retrospective case-control study to determine the relationship between cocaine use and DKA.

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SUBJECTS AND METHODS

Using a computer search of medical records of discharge diagnoses, we identified 720 hospital admissions for DKA in patients older than 18 years to Tampa General Hospital, a 1000-bed urban county tertiary care hospital in Tampa, Fla, from January 1, 1985, to December 31, 1994. We excluded subjects diagnosed as having DKA if they did not have either a pH less than 7.35 or a serum bicarbonate level less than 20 mmol/L, and either serum or urinary ketones. Criteria for cocaine use included either a documented history of cocaine use within the last year or positive results of a urine drug screening for cocaine metabolites during an admission. The users were initially identified through discharge diagnosis codings of "cocaine abuse" or "cocaine toxicity." Subsequently, patients with DKA who were found during the chart review to meet our criteria of cocaine use were included in the user group. The control group was an age- and sex-matched set of patients with DKA who were not found to be cocaine users by the above criteria.

We reviewed the medical records of all subjects for all DKA admissions. Subjects were considered to have a precipitating factor for DKA if there was evidence of infection, acute myocardial infarction, pancreatitis, trauma, or other acute medical illness believed to precipitate DKA. Subjects were considered to have complications related to diabetes (ie, retinopathy, nephropathy, neuropathy, etc) if they were recorded in the subject's chart. Data were extracted and compiled using scrambled medical record numbers to preserve anonymity. All data collected were kept anonymous and confidential. The characteristics of the users and the controls were analyzed using the SAS software system (SAS Institute Inc, Cary, NC), with χ^2 testing for categorical variables, 2-tailed *t* tests for continuous variables, and the Wilcoxon rank sum test for variables that failed to meet assumptions of normality. $P < .05$ was considered statistically significant. Multivariate regression analysis was performed on appropriately transformed variables, including all variables significant on bivariate comparison.

RESULTS

DEMOGRAPHICS

We identified 27 cocaine users with 102 admissions for DKA and 85 controls with 154 admissions. Demographic data are shown in **Table 1**. The 102 DKA admissions for users represented 14% of all adult admissions for DKA ($n = 720$) at Tampa General Hospital during the study period. Of the 27 cocaine users, 19 (70.4%) were women and 8 (29.6%) were men. The mean \pm SD age of the users on admission was 29.7 ± 6.6 years (age range, 18-60 years). No racial differences were found between the users and the controls (59.3% of the users and 65.9% of the controls were white; $P = .53$). The users had more frequent admissions for DKA than the controls (the mean number of admissions was 3.78 for users and 1.81 for the controls; $P = .03$).

DIABETIC HISTORY

The mean \pm SD duration of diabetes at the time of each admission for DKA was similar in both users and controls (9.0 ± 6.8 years vs 9.4 ± 7.2 years, respectively; $P = .58$). The use of insulin in patients known to be diabetic at the time of admission was similar for users and controls (97% of both users and controls with previously diagnosed diabetes were using insulin at the time of admission; $P = .97$). The frequency of complications related to diabetes was comparable for users and controls (25.9% and 28.2%, respectively; $P = .81$).

COCAINE USE

The form or route of administration of cocaine was reported in 32 (31.4%) of the admissions of cocaine users. Among the cocaine users for whom the form of cocaine use was documented, crack was reported the most frequently (in 17/32 admissions [53.1%]), followed by intravenous cocaine (in 9/32 admissions [28.1%]), and nasal insufflation (in 3/32 admissions [9.4%]). Findings from urine drug

screenings revealed cocaine metabolites in 28 (84.9%) of the 33 admissions in which they were ordered. Patterns of cocaine use, such as frequency of use, amount used, timing of use before admission, and duration of use, were reported too infrequently to permit further analysis.

CLINICAL FEATURES OF DKA

Precipitating Factors

The precipitating factors for DKA were different in cocaine users and controls. Intercurrent illnesses that could be considered precipitating factors for DKA were identified less frequently in user admissions than control admissions (14.7% vs 33.1%; $P < .001$). Infections were identified in 11.6% of users, compared with 26.6% of controls. Cocaine users were more likely than controls to report missing their dose of insulin for at least 1 day before admission (45.1% vs 24.7%; $P < .001$). Multivariate analysis found that the absence of a systemic illness and omission of insulin therapy were independent predictors of cocaine use.

Laboratory Evaluation

Laboratory data obtained from users and controls during admission to the emergency department were compared (**Table 2**). There were no significant differences between the 2 groups in measurements of serum sodium, chloride, bicarbonate, blood urea nitrogen, creatinine, pH, and anion gap. The mean \pm SD levels of serum glucose (32.9 ± 13.3 mmol/L [593.4 ± 238.9 mg/dL] vs 29.5 ± 10.3 mmol/L [531.1 ± 185.8 mg/dL]; $P = .03$) and potassium (5.2 ± 0.9 mmol/L vs 4.9 ± 0.9 mmol/L; $P < .01$) in the users were significantly higher than in the controls.

Clinical Course

Insulin drips were used in a similar percentage of admissions for users and controls (76% vs 78%, respectively;

Table 1. Demographic Characteristics of Patients With Diabetic Ketoacidosis (DKA)

Characteristic	Cocaine Users	Nonusers
No. of patients	27	85
Total DKA admissions, No.	102	154
Admissions per patient, mean (\pm SD), No.*	3.78 \pm 4.6	1.81 \pm 2.2
Age, mean (\pm SD) y	29.7 \pm 6.6	28.2 \pm 6.4
Sex, % female	70.4	64.5
Race, % white	59.3	65.9
Duration of diabetes, mean (\pm SD) y	9.0 \pm 6.8	9.4 \pm 7.2
Form of treatment for patients known to be diabetic at time of admission, % insulin	97.0	97.0
Frequency of diabetic complications, %	25.9	28.2

* $P = .03$.

$P = .65$), but for shorter periods in users (mean \pm SD duration, 18.3 \pm 11.8 hours for users and 22.7 \pm 18.7 hours for controls; $P = .04$). The mortality rate was similar in both groups (0.65% for users and 0.98% for controls; $P = .77$).

COMMENT

The recreational use of cocaine has increased in the last decade in the United States, with more than 30% of men and 20% of women between the ages of 26 and 34 years reporting prior cocaine use.¹⁹ We previously reported that 1% of adult patients admitted to our hospital were found to have cocaine metabolites in their urine.²⁰ In the current study, we found that 14% of all adult DKA admissions were related to cocaine use, comparable to the incidence of 13% found in a recent study from Atlanta.¹⁸ The prevalence of cocaine use has been reported in other inpatient populations, such as pregnant women (1%-17%),^{21,22} patients with psychiatric illness (up to 38%),²³ and patients who have experienced trauma (10%-54%).²⁴⁻²⁶ Although studies suggest no increased incidence of cocaine use in a cohort of young adults with type 1 diabetes mellitus, compared with other young adults without chronic illnesses,²⁷ we believe that patients with type 1 diabetes mellitus who use cocaine are more prone to develop ketoacidosis and require hospitalization. While our data do not directly prove this hypothesis, several key findings provide compelling arguments in its favor.

First, the patients with diabetes in our study who use cocaine were almost twice as likely to fail to take their insulin in the 24 hours prior to hospitalization. Many epidemiological studies of patients with DKA have pointed to insulin therapy omission as a major precipitating event, occurring with a frequency of 20% to 67%, depending on the population.²⁸⁻³² Explanations for the omission of insulin are rarely delineated. While some authors have cited lack of insulin availability or lack of appetite as major reasons for failing to take insulin,³² substance abuse has also been recognized in cases of insulin noncompliance.^{5,18,31} It is well known that during binge use, cocaine users may neglect various personal needs³³; we suggest that cocaine users with diabetes also fail to take their insulin.

Table 2. Laboratory Values on Admission*

	Cocaine Users	Nonusers
Sodium, mmol/L	133.7 \pm 6.2	133.4 \pm 6.1
Potassium, mmol/L†	5.2 \pm 0.9	4.9 \pm 0.9
Carbon dioxide, mmol/L	12.4 \pm 4.6	12.7 \pm 4.5
Urea nitrogen, mmol/L (mg/dL)	7.4 \pm 4.2 (20.6 \pm 11.8)	7.8 \pm 4.4 (21.8 \pm 12.4)
Creatinine, μ mol/L (mg/dL)	141.4 \pm 114.9 (1.6 \pm 1.3)	141.4 \pm 132.6 (1.6 \pm 1.5)
Glucose, mmol/L (mg/dL)†	32.9 \pm 13.3 (593.4 \pm 238.9)	29.5 \pm 10.3 (531.1 \pm 185.8)
Anion gap	23.5 \pm 7.2	23.0 \pm 5.9
pH	7.19 \pm 0.1	7.20 \pm 0.1

*All data are presented as mean (\pm SD).

† $P < .05$.

While the omission of insulin therapy alone may explain the increased admissions for DKA in cocaine users, the actions of cocaine on counterregulatory hormones also contribute to the development of DKA. We found that systemic illnesses, including infections, which are known to precipitate DKA, were less common in cocaine users than in the controls, suggesting that other factors contributed to the development of DKA in many cocaine users. Catecholamine levels, increased by cocaine use, profoundly affect carbohydrate metabolism by inhibiting pancreatic insulin secretion,³⁴ increasing the production of glucagon,³⁵ stimulating glycogenolysis and gluconeogenesis in the liver,^{36,37} activating lipolysis in the skeletal muscle,³⁸ and impairing the peripheral use of glucose.³⁹ In addition, catecholamines can stimulate ketogenesis through a variety of mechanisms, including increased hepatic production from augmented free fatty acid supply to the liver, a direct ketogenic effect on the liver (not accounted for by increased delivery of free fatty acids),⁴⁰ and decreased clearance of ketone bodies.⁴¹ Therefore, the use of cocaine can directly increase levels of counterregulatory hormones, leading to increased ketoacid production even in the absence of an underlying systemic illness. These effects are amplified in the absence of insulin, suggesting that patients who use cocaine and fail to take their insulin may be especially predisposed to DKA because of enhanced adrenergic activity.

In our study, the resolution of DKA was not protracted in cocaine users compared with controls. Even though cocaine users had higher mean glucose levels on admission, which may have been related to increased levels of catecholamines and glucocorticoids, DKA in cocaine users responded well to treatment and actually required shorter insulin infusions. We postulate that rapidly declining cocaine levels allow counterregulatory hormone levels to return to normal. Because cocaine users are less likely to have underlying systemic illnesses, DKA in these patients can be expected to respond promptly to appropriate therapy.

We recognize that our study is a preliminary one with several limitations. Because we identified cocaine users based on chart documentation and the results of urine drug screenings that were not systematically conducted on all patients with DKA, our group of cocaine users was limited to patients who were screened for drug

abuse. Likewise, we recognize that documenting the failure to take insulin depends on self-reporting and may not be completely reliable. Given the exploratory nature of our work, our findings are to be interpreted as preliminary and in need of further validation. Nevertheless, given the limited information in the literature about drug use and DKA, we believe that this study provides important information about a previously unrecognized risk factor for DKA. Further studies examining the association between substance abuse and DKA should be conducted to confirm our results.

We were surprised to find a paucity of data regarding substance abuse in patients with diabetes and encourage clinicians taking care of such patients to assess whether they abuse drugs. Patients with diabetes who use cocaine should be counseled about the effect of cocaine use on controlling diabetes. Cocaine use should be regarded as a risk factor for DKA, particularly for patients with multiple episodes of DKA.

CONCLUSIONS

In our study, nearly 1 in 7 adults admitted with DKA was a cocaine user. Cocaine users were more likely to have omitted insulin doses and less likely to have had a precipitating systemic illness at the time of admission for DKA. Cocaine users were found to have more frequent admissions for DKA. We believe that either because of its association with more frequent omission of insulin therapy or because of its effects on counterregulatory hormone levels, cocaine use is a risk factor for DKA.

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