Journal of Clinical & Translational Endocrinology 9 (2017) 1–7

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Original research

# Active cocaine use does not increase the likelihood of hyperglycemic crisis

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ARTICLE INFO

*Article history:*
Received 15 December 2016
Received in revised form 17 May 2017
Accepted 30 May 2017

*Keywords:*
Diabetes mellitus
Diabetic ketoacidosis
Hyperosmolar hyperglycemic state
Cocaine
Substance abuse

ABSTRACT

*Objective:* Hyperglycemic crisis encompasses a group of diabetes emergencies characterized by insulin deficiency with high morbidity and mortality. Cocaine use is increasingly prevalent in the United States and may be associated with increased risk of diabetic ketoacidosis. The objective was to determine if active cocaine use at hospital admission could be considered a risk factor for development of hyperglycemic crisis.

*Methods:* A retrospective case-control analysis was performed on 950 inpatients with hyperglycemia at an urban academic hospital. Patients admitted with non-emergent hyperglycemia were compared to patients who met criteria for diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and hyperosmolar ketoacidosis (HK), based on the absence or presence of cocaine metabolites on urine toxicology screen. Outcomes included frequency of cocaine use in patients with DKA, HHS, HK, and non-emergent hyperglycemia; phenotypic characteristics of cocaine users vs. non-users with hyperglycemia; phenotypic characteristics of patients with hyperglycemic crisis vs. non-emergent hyperglycemia.

*Results:* 950 patients were admitted with hyperglycemia, 133 of which met criteria for hyperglycemic crisis. There was no significant difference in the frequency of cocaine use in individuals with non-emergent hyperglycemia compared to individuals with hyperglycemic crisis (16.9% vs. 17.2%, p = 0.90). 16.9% of patients with DKA, 16.4% of patients with HHS, and 6.4% of patients with HK were cocaine users.

*Conclusions:* We found no association between active cocaine use at the time of hospital admission and development of hyperglycemic crisis, when compared to non-emergent hyperglycemia. The role of routine screening for cocaine use in patients with hyperglycemic crisis is unclear.



## Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most common diabetes emergencies [1]. The overlap syndrome of hyperosmolar ketoacidosis (HK) is less common, but along with HHS, is associated with higher mortality than DKA [2]. These three conditions, which constitute the spectrum of hyperglycemic crisis, result from absolute or relative insulin deficiency in the setting of excess counter-regulatory hormone production [3]. The pathophysiological mechanisms are best described in DKA, in which acute insulin deficiency results in an increase in free fatty acid production. This leads to excess ketone body production, reduced urinary clearance, and resultant metabolic acidosis [4]. HHS is characterized by marked hyperglycemia and hyperosmolarity, the combination of which leads to osmotic diuresis, volume depletion, hyperviscosity and ultimately, tissue hypoperfusion and worsening insulin resistance [5].

Cocaine has previously been described as contributing to worsening hyperglycemia through a combination of direct increase in counter-regulatory hormones and indirect promotion of insulin omission [6–8]. Prior clinical studies of the relationship between

*Abbreviations:* BMI, body mass index; DKA, diabetic ketoacidosis; HgbA1C, hemoglobin A1C; HHS, hyperosmolar hyperglycemic state; HK, hyperosmolar ketoacidosis; IDR, inpatient diabetes repository; T1D, type 1 diabetes.

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http://dx.doi.org/10.1016/j.jcte.2017.05.004
2214-6237/

cocaine and hyperglycemic crisis have reported a possible association between patient self-reported and laboratory confirmed cocaine use and subsequent development of DKA. However, a direct association between the two is not well established, given limitations in prior studies, which include variable definitions of hyperglycemic crisis, an exclusive focus on DKA and the fact that concomitant cocaine use has not necessarily been strictly confirmed at the time of admission for hyperglycemic crisis.

In order to address this uncertainty, we conducted a retrospective case-control study to further our understanding as to whether active cocaine use, confirmed through urine toxicology screening at the time of hospital admission, could be considered a risk factor for development of hyperglycemic crisis.

We hypothesized that confirmed cocaine use (urine cocaine metabolites being present at the time of admission with hyperglycemia) would be encountered more frequently in patients admitted with hyperglycemic crisis compared with patients admitted with non-emergent hyperglycemia. Secondarily, we hypothesized that individuals with hyperglycemic crisis who use cocaine might exhibit different phenotypic features, such as more severe hyperglycemia, compared to those not using cocaine. Because so little is known about the role of cocaine in the clinical course of HHS and HK, we also hypothesized that there may be differential effects of cocaine use on the patients' metabolic characteristics depending on whether individuals were diagnosed with DKA, HHS or HK. Through these questions, we hoped to define clinical features that would lead clinicians to suspect cocaine as a contributing risk factor in hyperglycemic crisis.

## Methods

We extracted a limited data set from an established, Institutional Review Board-approved inpatient diabetes repository (IDR) of approximately 40,000 individual subjects admitted with hyperglycemia at Boston Medical Center, an urban academic hospital with a large "safety-net population." We identified a sub-group of 950 individuals admitted with both hyperglycemia (blood glucose > 250 mg/dL) and available urine toxicology screens for cocaine between July 1, 2004, and December 31, 2010.

Using this dataset, we performed a retrospective case-control analysis to compare a group of individuals with hyperglycemic crisis to a group of hyperglycemic individuals without crisis. We included individuals between the ages of 18 and 65 (age limits were pre-determined by the available IDR dataset) with blood glucose > 250 mg/dL on emergency department laboratory evaluation with available urine toxicology screens at the time of the admission of interest. We defined a group of 133 individuals from all ethnic groups who met diagnostic criteria for DKA, HHS or HK as the hyperglycemic crisis group (cases). The DKA group was defined by the presence of all of the following criteria: venous or arterial pH < 7.3 and/or serum bicarbonate < 15 mmol/L, ketonuria, and anion gap > 14; the HHS group was defined by both blood glucose > 600 mg/dL and measured serum osmolarity > 340 mOsm/kg H2O or effective serum osmolarity > 320 mOsm/kg H2O; the HK group was defined by venous or arterial pH < 7.3 and/or serum bicarbonate < 15 mmol/L, ketonuria, and measured serum osmolarity > 340 mOsm/kg H2O or effective osmolarity > 320 mOsm/kg $H_2O$. Effective osmolarity was defined as: 2[measured $Na^+$(mmol/L)] + glucose (mg/dL)/18. Total osmolarity was defined as: 2[measured $Na^+$ (mmol/L)] + glucose (mg/dL)/18 + BUN/2.8. It is important to note that based on these criteria, certain individuals may meet criteria for more than one diagnosis and as a result were "double counted" in subsequent analyses. For example, a patient meeting criteria for HK may meet all of the criteria for DKA but if blood sugar is less than 600 mg/dL would not meet all of the criteria for HHS, so would be included in the analyses for both HK and DKA, but not HHS. Individuals with hyperglycemia not meeting the aforementioned criteria for hyperglycemic crisis were designated as subjects for the non-emergent hyperglycemia control group (controls).

We deliberately excluded individuals without available urine toxicology data to ensure that antecedent cocaine exposure was confirmed. Cocaine exposure was defined as the presence of cocaine metabolites on urine toxicology screen on presentation to the emergency department or admission to the intensive care unit. Serum toxicology screens were not included as urine toxicology screening is the routine practice at our institution. The decision to perform toxicology screening was at the discretion of the emergency department and intensive care unit teams.

We performed multiple analyses in this group of hyperglycemic individuals who had undergone urine toxicology testing designed to explore the hypotheses that cocaine use is more likely to be associated with DKA, HHS, and HK than non-emergent hyperglycemia; that cocaine acts as an effect modifier for the relationship between demographic factors and hyperglycemic crisis; and that there may be phenotypic differences between hyperglycemic crisis cocaine users and hyperglycemic crisis non-users.

We first describe the hyperglycemic crisis and non-hyperglycemic crisis groups in terms of demographic characteristics, laboratory values and cocaine use. The categorical variables are presented as counts and percentages, and the continuous variables as means, standard deviations, medians and ranges. Fisher's exact test was used to compare categorical factors across the groups and *t*-test was used to compare continuous variables. We describe the hyperglycemic crisis subgroups – DKA, HHS and HK – in terms of demographic characteristics, laboratory values and cocaine use.

A multivariable logistic regression was used to evaluate the relationship between cocaine use and hyperglycemic crisis controlling for possible confounders: age, gender, race (self-identified by patient), education, primary language, body mass index (BMI) and hemoglobin A1C (HgbA1C). Odds ratios with 95% confidence intervals are reported. To examine potentiation effect modification by gender, race and education, we added multiplicative interaction terms with cocaine use to the model.

To examine potential phenotypic differences between hyperglycemic crisis cocaine users and non-users, we used Fisher's exact test for categorical variables and *t*-test for continuous variables. All analyses were performed using SAS v9.3. P values < 0.05 were considered statistically significant.

## Results

### *Demographics*

Of the 950 patients admitted with hyperglycemia and available urine toxicology data between July 1, 2004, and December 31, 2010, 133 patients presented with hyperglycemic crisis. Their clinical characteristics are shown in Table 1. Compared to those admitted with non-emergent hyperglycemia, those with hyperglycemic crisis were younger (44.9 vs. 47.7 years, p = 0.008). There were more men and black patients admitted across both groups, but a higher percentage of patients with hyperglycemic crisis were black compared to those without crisis (61% vs. 48%, p = 0.035). Patients with hyperglycemic crisis were more likely to have worse baseline glycemic control as determined by HgbA1C obtained during admission [11.7% (104 mmol/mol) vs. 10% (86 mmol/mol), p < 0.001] and more significant hyperglycemia on admission (average blood glucose 707.9 vs. 406.5 mg/dL, p < 0.001). The groups did not differ in primary language spoken, education level, BMI, or cocaine use.

**Table 1**
Clinical and biochemical characteristics of patients with diabetes stratified by hyperglycemic crisis and non-emergent hyperglycemia.

| Characteristic | Overall (N = 950) | Crisis (N = 133) | No Crisis (N = 817) | p-value |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean ± SD | 47.3 ± 11.4 | 44.9 ± 11.3 | 47.7 ± 11.3 | 0.008 |
| Gender | | | | |
| Male | 626 (65.9%) | 87 (65.4%) | 539 (66.0%) | 0.922 |
| Female | 324 (34.1%) | 46 (34.6%) | 278 (34.0%) | |
| Race | | | | |
| White | 235 (24.8%) | 23 (17.4%) | 212 (26.0%) | 0.035 |
| Black | 476 (50.3%) | 81 (61.4%) | 395 (48.5%) | |
| Hispanic | 175 (18.5%) | 19 (14.4%) | 156 (19.2%) | |
| Other | 60 (6.3%) | 9 (6.8%) | 51 (6.3%) | |
| Language | | | | |
| English | 831 (87.5%) | 110 (82.7%) | 721 (88.2%) | 0.089 |
| Non-English | 119 (12.5%) | 23 (17.3%) | 96 (11.8%) | |
| Education | | | | |
| 8th Grade or Less | 92 (11.1%) | 16 (13.4%) | 76 (10.7%) | 0.155 |
| Some HS | 269 (32.4%) | 46 (38.7%) | 223 (31.4%) | |
| HS – Some College | 323 (38.9%) | 36 (30.3%) | 287 (40.4%) | |
| College Graduate | 146 (17.6%) | 21 (17.6%) | 125 (17.6%) | |
| Height (in) | | | | |
| Mean ± SD | 67.2 ± 4.3 | 68.1 ± 5.4 | 67.1 ± 4.1 | 0.078 |
| Weight (lb) | | | | |
| Mean ± SD | 193.1 ± 58.9 | 183.7 ± 53.2 | 194.4 ± 59.6 | 0.177 |
| BMI | | | | |
| Mean ± SD | 29.8 ± 8.7 | 27.8 ± 7.4 | 30.1 ± 8.9 | 0.064 |
| A1c | | | | |
| Mean ± SD | 10.3 ± 2.9 | 11.7 ± 3.1 | 10.0 ± 2.8 | <0.001 |
| Anion Gap | | | | |
| Mean ± SD | 15.5 ± 6.6 | 20.9 ± 7.1 | 14.8 ± 6.2 | <0.001 |
| Creatinine | | | | |
| Mean ± SD | 1.6 ± 1.5 | 2.0 ± 1.4 | 1.5 ± 1.6 | 0.001 |
| Potassium | | | | |
| Mean ± SD | 4.4 ± 0.9 | 4.9 ± 1.1 | 4.4 ± 0.8 | <0.001 |
| Chloride | | | | |
| Mean ± SD | 98.4 ± 7.9 | 94.3 ± 9.9 | 99.0 ± 7.4 | <0.001 |
| Osmolarity | | | | |
| Mean ± SD | 300.3 ± 16.8 | 320.0 ± 28.2 | 297.1 ± 11.2 | <0.001 |
| Ph | | | | |
| Mean ± SD | 7.3 ± 0.1 | 7.2 ± 0.1 | 7.3 ± 0.1 | <0.001 |
| Median and Range | 7.4 (6.6–7.6) | 7.3 (6.8–7.5) | 7.4 (6.6–7.6) | |
| Na (mEq/l) | | | | |
| Mean ± SD | 137.7 ± 5.9 | 140.4 ± 8.2 | 137.3 ± 5.3 | <0.001 |
| Glucose (mg/dl) | | | | |
| Mean ± SD | 448.7 ± 224.2 | 707.9 ± 377.1 | 406.5 ± 150.7 | <0.001 |
| Ketonuria | | | | |
| Yes | 226 (23.8%) | 89 (66.9%) | 137 (16.8%) | <0.001 |
| No | 724 (76.2%) | 44 (33.1%) | 680 (83.2%) | |
| Bicarbonate (mEq/dl) | | | | |
| Mean ± SD | 22.3 ± 6.1 | 17.9 ± 6.8 | 23.1 ± 5.6 | <0.001 |
| Cocaine Use | | | | |
| Yes | 161 (16.9%) | 23 (17.3%) | 138 (16.9%) | 0.901 |
| No | 789 (83.1%) | 110 (82.7%) | 679 (83.1%) | |

*Hyperglycemic crisis*

Of the 133 patients admitted with hyperglycemic crisis, 77 met criteria for DKA (58%), 67 for HHS (50%), and 15 for HK (11%), with 26 patients meeting diagnostic criteria for inclusion in more than one group (Table 2). The patients who met criteria for inclusion in more than one group were included in the analysis for each of the groups into which they belonged, given the expected overlap in certain patients with hyperglycemic crisis. Overall, patients with DKA were younger than those with HHS and HK. Male gender was predominant in all groups, but the gender discrepancy was largest in the HHS and HK groups. Patients with HHS and HK had higher BMIs and had worse glycemic control (HgbA1c) than patients with DKA. As would be expected, serum osmolarity was higher in the HHS and HK groups, while pH was significantly lower in the DKA and HK groups. Those with HHS presented with the highest mean glucose concentrations, followed by HK and then DKA (960, 736, and 509 mg/dL, respectively).

*Cocaine use*

A comparison between cocaine users and non-users was performed to assess for possible phenotypic differences between the two groups. Among the 950 patients analyzed, 161 had a urine toxicology screen positive for cocaine on admission (16.9%), with no significant difference between the hyperglycemic crisis and non-emergent hyperglycemia groups (17.2% and 16.9%, $p = 0.90$) (Table 3). There was no age difference between users and non-users. Men were more likely to use cocaine than women (66.5% vs. 33.5%). 61.9% of cocaine users were black, while only 50.3% of the total population was black. Cocaine use was also positively correlated with patients who spoke English as their primary language and lower education level. There was no difference in BMI, baseline HgbA1C or presenting lab values between cocaine users and non-users. However, glucose concentrations on admission were significantly higher in the cocaine users (480.9 vs. 442.1 mg/dL, $p = 0.045$).

**Table 2**
Clinical and biochemical characteristics of patients with diabetic ketoacidosis, hyperosmolar hyperketotic state, and hyperosmolar ketoacidosis.

| Characteristic | DKA (N = 77) | HHS (N = 67) | HK (N = 15) |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD | 43.1 ± 12.1 | 46.7 ± 10.1 | 46.9 ± 11.4 |
| Gender | | | |
| Male | 49 (63.6%) | 48 (71.6%) | 12 (80%) |
| Female | 28 (36.4%) | 19 (28.4%) | 3 (20%) |
| Race | | | |
| White | 18 (23.4%) | 7 (10.6%) | 3 (20%) |
| Black | 44 (57.1%) | 44 (66.7%) | 9 (60%) |
| Hispanic | 12 (15.6%) | 9 (13.6%) | 2 (13.3%) |
| Other | 3 (3.9%) | 6 (9.1%) | 1 (6.7%) |
| Language | | | |
| English | 63 (81.8%) | 56 (83.6%) | 12 (80%) |
| Non-English | 14 (18.2%) | 11 (16.4%) | 3 (20%) |
| Education | | | |
| 8th Grade or Less | 6 (8.8%) | 11 (17.7%) | 1 (7.7%) |
| Some HS | 26 (38.2%) | 23 (37.1%) | 4 (30.8%) |
| HS – Some College | 24 (35.3%) | 16 (25.8%) | 4 (30.8%) |
| College Graduate | 12 (17.6%) | 12 (19.4%) | 4 (30.8%) |
| Height (in) | | | |
| Mean ± SD | 68 ± 5 | 68.5 ± 6 | 69.5 ± 5.7 |
| Weight (lb) | | | |
| Mean ± SD | 171.4 ± 46.1 | 199.3 ± 56.2 | 194.3 ± 41.7 |
| BMI | | | |
| Mean ± SD | 26.1 ± 7.2 | 30 ± 7.1 | 28.9 ± 6.9 |
| A1c | | | |
| Mean ± SD | 11.5 ± 3.3 | 12.3 ± 3 | 14.4 ± 3 |
| Anion Gap | | | |
| Mean ± SD | 21.9 ± 6.8 | 20.5 ± 7.8 | 30.4 ± 5.1 |
| Creatinine | | | |
| Mean ± SD | 1.8 ± 1.4 | 2.4 ± 1.4 | 2.6 ± 1.5 |
| Potassium | | | |
| Mean ± SD | 4.9 ± 1.1 | 5.1 ± 1.3 | 5.7 ± 1.5 |
| Chloride | | | |
| Mean ± SD | 95.7 ± 9.7 | 92.2 ± 10 | 95.6 ± 12.1 |
| Osmolarity | | | |
| Mean ± SD | 304.7 ± 20.1 | 340.7 ± 23.1 | 336.2 ± 18 |
| Ph | | | |
| Mean ± SD | 7.2 ± 0.1 | 7.3 ± 0.1 | 7.2 ± 0.2 |
| Na (mEq/l) | | | |
| Mean ± SD | 138.2 ± 7.8 | 143.7 ± 8.3 | 147.7 ± 9.7 |
| Glucose (mg/dl) | | | |
| Mean ± SD | 508.8 ± 199.7 | 959.6 ± 364.9 | 735.7 ± 222.2 |
| Ketonuria | | | |
| Yes | 77 (100%) | 23 (34.3%) | 15 (100%) |
| No | 0 (0.0%) | 44 (65.7%) | 0 (0.0%) |
| Bicarbonate (mEq/dl) | | | |
| Mean ± SD | 15.2 ± 6.3 | 20.7 ± 6.5 | 12.9 ± 5.8 |
| Cocaine Use | | | |
| Yes | 13 (16.9%) | 11 (16.4%) | 1 (6.7%) |
| No | 64 (83.1%) | 56 (83.6%) | 14 (93.3%) |

*Cocaine use and hyperglycemic crisis*

13 out of 77 patients with DKA (16.9%), 11 out of 67 patients with HHS (16.4%), and 1 out of 15 patients with HK (6.7%) were cocaine users (Table 4). Patients with hyperglycemic crisis differed only in their mean bicarbonate levels, which were significantly lower in the group who did not use cocaine compared to the group who did use cocaine. They did not differ significantly in any of the other studied variables regardless of whether or not they used cocaine.

*Predictors of hyperglycemic crisis*

Multivariable analysis was performed to identify possible predictors of hyperglycemic crisis (Fig. 1). There was no significant interaction of cocaine use with gender, race or education. Cocaine use was not significantly associated with hyperglycemic crisis in either gender (OR 0.90, 95% CI 0.28–2.92, p = 0.86 in men; OR 0.43, 95% CI 0.05–3.82, p = 0.45 in women). Being non-English speaking or black resulted in a non-significant increase in the odds of developing hyperglycemic crisis. Specifically, within the DKA group there was a possible non-significant positive association between males who used cocaine and development of DKA (OR 1.83, 95% CI 0.51–6.61, p = 0.36) and a similarly possible non-significant negative association between females who used cocaine and development of DKA (OR 0.54, 95% CI 0.06–5.13, p = 0.59). There was also a possible non-significant negative association between males who used cocaine and subsequently developed HHS (OR 0.46, 95% CI 0.13–1.68, p = 0.24). There were no female cocaine users who presented with HHS and only one patient who used cocaine who presented with HK, which significantly limits analyses of these patients.

## Discussion

Hormones that antagonize insulin action are known as counter-regulatory hormones and include various hormones such as growth hormone, cortisol, glucagon and catecholamines. In the appropriate metabolic milieu they promote hyperglycemia and ketogenesis [9]. Conditions such as acute myocardial infarction, major infection and trauma are associated with hyperglycemic crisis, partly through an increase in these counter-regulatory "stress" hormones [10]. Cocaine also has a direct stimulatory effect on counter-regulatory hormone secretion. In rodents, it has been reported to stimulate release of catecholamines from the adrenal glands [6]. In humans, increases in serum cocaine concentrations have been reported to directly correlate with increases in serum ACTH concentration after intravenous cocaine administration [11,12]. Given these potentiating metabolic effects, it is conceivable that cocaine use may predispose patients to the development of hyperglycemia and/or hyperglycemic crisis.

Prior studies suggesting cocaine use as a cause of DKA have been limited and varied in their methods of confirming cocaine use. These limitations have included patient self-report of substance abuse in the prior year, patient self-report of substance abuse in the days prior to admission, and positive toxicology screens at varying time intervals [7,8,13]. None of the prior studies exclusively included patients who were determined, through direct measurement of urine cocaine metabolites, to be actively using cocaine at the time of presentation to the hospital with hyperglycemia. We believe that a significant strength of our study is that we only included subjects with a positive urine toxicology screen on admission in the cocaine user group, and all patients required a urine toxicology screen for inclusion. We also included a reasonably large sample of 950 patients with both hyperglycemia and available urine toxicology screens, of which 161 used cocaine and 133 met criteria for hyperglycemic crisis.

Our study found no difference in the frequency of active cocaine use between patients admitted with non-emergent hyperglycemia and hyperglycemic crisis. The 17.2% prevalence rate of cocaine use in subjects with hyperglycemic crisis is slightly higher than reported in previous studies (~14%) [7,8,13]. However, the populations in each study are not entirely comparable to ours, and the age limits in our population may have affected this prevalence. Within the hyperglycemic crisis groups, cocaine use was similarly frequent in patients with DKA (16.9%) and HHS (16.4%), while less frequent in patients with HK (6.4%). To the best of our knowledge, the prevalence of cocaine use in HK has not previously been reported. However, we cannot draw any substantial conclusions from the extremely small number of HK subjects in our study. The use of multivariable analysis confirmed that even within specific subgroups there was no significant association between cocaine use and hyperglycemic crisis. There was also no laboratory difference

**Table 3**
Clinical and biochemical characteristics of patients with diabetes stratified by cocaine use.

| Characteristic | Overall (N = 950) | Cocaine Use (N = 161) | No Cocaine (N = 789) | p-value |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean ± SD | 47.3 ± 11.4 | 46.7 ± 9.5 | 47.4 ± 11.7 | 0.475 |
| Gender | | | | |
| Male | 626 (65.9%) | 107 (66.5%) | 519 (65.8%) | 0.927 |
| Female | 324 (34.1%) | 54 (33.5%) | 270 (34.2%) | |
| Race | | | | |
| White | 235 (24.8%) | 31 (19.3%) | 204 (26%) | <0.001 |
| Black | 476 (50.3%) | 97 (60.2%) | 379 (48.3%) | |
| Hispanic | 175 (18.5%) | 32 (19.9%) | 143 (18.2%) | |
| Other | 60 (6.3%) | 1 (0.6%) | 59 (7.5%) | |
| Language | | | | |
| English | 831 (87.5%) | 154 (95.7%) | 677 (85.8%) | <0.001 |
| Non-English | 119 (12.5%) | 7 (4.3%) | 112 (14.2%) | |
| Education | | | | |
| 8th Grade or Less | 92 (11.1%) | 14 (9.3%) | 78 (11.5%) | 0.002 |
| Some HS | 269 (32.4%) | 60 (40%) | 209 (30.7%) | |
| HS – Some College | 323 (38.9%) | 64 (42.7%) | 259 (38.1%) | |
| College Graduate | 146 (17.6%) | 12 (8%) | 134 (19.7%) | |
| Height (in) | | | | |
| Mean ± SD | 67.2 ± 4.3 | 67.4 ± 4.5 | 67.2 ± 4.3 | 0.665 |
| Weight (lb) | | | | |
| Mean ± SD | 193.1 ± 58.9 | 194.8 ± 71.7 | 192.7 ± 56.1 | 0.764 |
| BMI | | | | |
| Mean ± SD | 29.8 ± 8.7 | 30 ± 10.8 | 29.7 ± 8.2 | 0.832 |
| A1c | | | | |
| Mean ± SD | 10.3 ± 2.9 | 10.3 ± 2.8 | 10.3 ± 2.9 | 0.903 |
| Anion Gap | | | | |
| Mean ± SD | 15.5 ± 6.6 | 15 ± 5.6 | 15.6 ± 6.7 | 0.404 |
| Creatinine | | | | |
| Mean ± SD | 1.6 ± 1.5 | 1.8 ± 1.9 | 1.6 ± 1.5 | 0.141 |
| Potassium | | | | |
| Mean ± SD | 4.4 ± 0.9 | 4.5 ± 0.9 | 4.4 ± 0.9 | 0.428 |
| Chloride | | | | |
| Mean ± SD | 98.4 ± 7.9 | 97.9 ± 8.4 | 98.5 ± 7.8 | 0.391 |
| Osmolarity | | | | |
| Mean ± SD | 300.3 ± 16.8 | 300.6 ± 16.3 | 300.3 ± 16.9 | 0.814 |
| Ph | | | | |
| Mean ± SD | 7.3 ± 0.1 | 7.3 ± 0.1 | 7.3 ± 0.1 | 0.723 |
| Na (mEq/l) | | | | |
| Mean ± SD | 137.7 ± 5.9 | 136.9 ± 6 | 137.9 ± 5.8 | 0.074 |
| Glucose (mg/dl) | | | | |
| Mean ± SD | 448.7 ± 224.2 | 480.9 ± 211.8 | 442.1 ± 226.2 | 0.045 |
| Ketonuria | | | | |
| Yes | 226 (23.8%) | 36 (22.4%) | 190 (24.1%) | 0.685 |
| No | 724 (76.2%) | 125 (77.6%) | 599 (75.9%) | |
| Bicarbonate (mEq/dl) | | | | |
| Mean ± SD | 22.3 ± 6.1 | 22.9 ± 6.1 | 22.2 ± 6.1 | 0.365 |
| DKA | | | | |
| Yes | 77 (8.1%) | 13 (8.1%) | 64 (8.1%) | 0.999 |
| No | 873 (91.9%) | 148 (91.9%) | 725 (91.9%) | |
| HHS | | | | |
| Yes | 67 (7.1%) | 11 (6.8%) | 56 (7.1%) | 0.999 |
| No | 883 (92.9%) | 150 (93.2%) | 733 (92.9%) | |
| HK | | | | |
| Yes | 15 (1.6%) | 1 (0.6%) | 14 (1.8%) | 0.488 |
| No | 935 (98.4%) | 160 (99.4%) | 775 (98.2%) | |
| Hyperglycemic Crisis | | | | |
| Yes | 133 (14%) | 23 (14.3%) | 110 (13.9%) | 0.901 |
| No | 817 (86%) | 138 (85.7%) | 679 (86.1%) | |

between cocaine users and non-users, apart from the intriguing finding of higher glucose concentrations at presentation in cocaine users. This may further support the generally accepted idea that hyperglycemia is only a part of the pathophysiological process underlying hyperglycemic crisis, given that we show here that cocaine independently promotes hyperglycemia, even though the severity of hyperglycemic crisis is not worsened by cocaine use. Some of the subjects included in the study population likely did not have a pre-existing diagnosis of diabetes, as indicated by HgbA1C less than 6.5%, so it is possible that cocaine could be a precipitant of new onset hyperglycemia and potentially hyperglycemic crisis in this group, though a larger sample size would be needed to further evaluate this possible relationship. Given the likelihood that glucose levels were not in equilibrium prior to the time of admission, the higher average HgbA1c in the crisis groups is difficult to interpret, although there is data that suggests that the HgbA1c is weighted preferentially towards more recent glycemic control (approximately 2 weeks) than prior ambient glucose, so the difference is possibly due to recent glycemic trends.

Our results suggest that cocaine use does not appear to be an acute precipitant of hyperglycemic crisis. Warner et al. suggested that insulin omission while actively using cocaine, in combination with increased counter-regulatory hormone concentrations, may be a primary precipitating cause of DKA [8]. However, they only included patients in DKA stratified by cocaine use vs. no cocaine use, so it is not known if similar findings would have been reported

**Table 4**
Clinical and biochemical characteristics of patients with hyperglycemic crisis stratified by cocaine use.

| Characteristic | Cocaine Use (N = 23) | No Cocaine (N = 110) | p-value |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD | 45.1 ± 8.9 | 44.8 ± 11.8 | 0.926 |
| Gender | | | |
| Male | 19 (82.6%) | 68 (61.8%) | 0.090 |
| Female | 4 (17.4%) | 42 (38.2%) | |
| Race | | | |
| White | 5 (21.7%) | 18 (16.5%) | 0.601 |
| Black | 15 (65.2%) | 66 (60.6%) | |
| Hispanic | 3 (13%) | 16 (14.7%) | |
| Other | 0 (0%) | 9 (8.3%) | |
| Language | | | |
| English | 22 (95.7%) | 88 (80%) | 0.125 |
| Non-English | 1 (4.3%) | 22 (20%) | |
| Education | | | |
| 8th Grade or Less | 1 (4.8%) | 15 (15.3%) | 0.350 |
| Some HS | 11 (52.4%) | 35 (35.7%) | |
| HS – Some College | 7 (33.3%) | 29 (29.6%) | |
| College Graduate | 2 (9.5%) | 19 (19.4%) | |
| Height (in) | | | |
| Mean ± SD | 68 ± 7.7 | 68.1 ± 4.8 | 0.917 |
| Weight (lb) | | | |
| Mean ± SD | 196 ± 57.4 | 181.4 ± 52.6 | 0.431 |
| BMI | | | |
| Mean ± SD | 28.4 ± 8.1 | 27.6 ± 7.3 | 0.778 |
| A1c | | | |
| Mean ± SD | 12.1 ± 2.6 | 11.6 ± 3.2 | 0.645 |
| Anion Gap | | | |
| Mean ± SD | 19.5 ± 7.1 | 21 ± 7.2 | 0.568 |
| Creatinine | | | |
| Mean ± SD | 1.9 ± 0.9 | 2 ± 1.5 | 0.614 |
| Potassium | | | |
| Mean ± SD | 4.9 ± 1.1 | 4.9 ± 1.1 | 0.999 |
| Chloride | | | |
| Mean ± SD | 92.6 ± 8.4 | 94.6 ± 10.2 | 0.363 |
| Ph | | | |
| Mean ± SD | 7.3 ± 0.1 | 7.2 ± 0.1 | 0.162 |
| Glucose (mg/dl) | | | |
| Mean ± SD | 671.5 ± 294.7 | 715.5 ± 392.9 | 0.613 |
| Bicarbonate (mEq/dl) | | | |
| Mean ± SD | 23.2 ± 6.8 | 17.3 ± 6.6 | 0.019 |

in a control group without hyperglycemic crisis, or in individuals with HHS or HK. In particular, without accurate documentation of active cocaine use at the time of admission for DKA, it is difficult to truly establish or refute any relationship between the two.

Overall, the percentage of cocaine use in our hyperglycemic subjects was similar to the reported national prevalence (16.9% vs. 17.1%) [14]. Current estimates for lifetime prevalence of cocaine use from the National Survey of Drug Use and Health in people ages 26 and over is 17.1%. The lifetime prevalence of cocaine use continues to increase in the United States, with the largest increase in the late teenage years and early adulthood. This is a time at which patients with type 1 diabetes (T1D) are particularly vulnerable and at risk for hyperglycemic crisis. Studies in different countries have reported variable prevalence of cocaine use in children with T1D, though overall decreased use compared to healthy peers has been reported [15,16]. However, no similar studies exist in the United States population and we did not include this population in our analysis. To the best of our knowledge, there are no prior large studies exploring cocaine use in a diverse adult population with hyperglycemia and/or diabetes.

There are several limitations inherent to our retrospective study design. Firstly, we were unable to identify the cause of hyperglycemic crisis in our cohort given a lack of complete available data. Secondly, it is also difficult to ascertain the "percent attributable exposure" from cocaine, especially as it is likely that a fair amount of the patients admitted with hyperglycemic crisis also had concomitant insulin omission. We were unable to include this data in our analysis, which makes it difficult to be sure how much of this could be attributed directly to cocaine versus simple insulin omission. Prior studies have suggested that urban populations are more likely to develop hyperglycemic crisis as a result of insulin omission, with the assumption that cocaine use is associated with higher frequency of insulin omission [7,8]. It is also plausible that active cocaine use may predispose patients to development of infections. Although we report a higher percentage of subjects with hyperglycemic crisis who were active cocaine users than prior studies, this percentage did not differ from cocaine use in subjects with non-emergent hyperglycemia. There is no clear reason why insulin omission would differ significantly between these two groups, though we did not have qualitative data on individual cocaine habits that would help to determine if cocaine use patterns impact insulin omission. For example, it is plausible that certain cocaine users may have habits, such as increased oral hydration while intoxicated, which may protect them from the development of crisis. One would expect that substance abuse would result in an increased tendency towards insulin omission while intoxicated, which in turn would be expected to be associated with development of hyperglycemic crisis. However, this was perhaps surprisingly not apparent in our population.

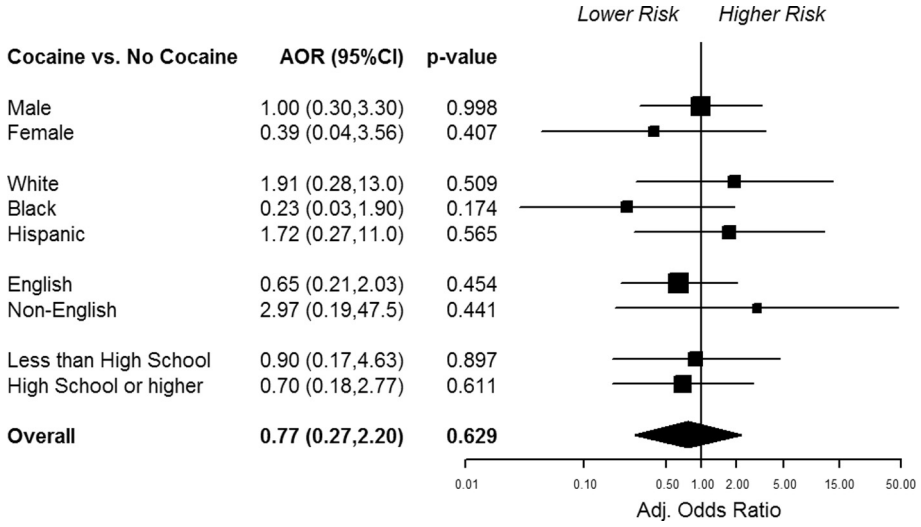


**Fig. 1.** Multivariable logistic regression analysis of variables associated with hyperglycemic crisis in cocaine users.

We were unable to obtain length of stay or illness severity data on the included patients. In addition, our subjects were identified as having diabetes by admission ICD-9 codes, limiting our ability to accurately assign specific type 1 or type 2 diabetes diagnoses to evaluate those relationships. We also were limited to patients between the ages of 18 and 65 based on the available data in the IDR, which may have affected rates of hyperglycemic crisis and contributed to the lack of difference in the average ages among the hyperglycemic crisis groups. As a result, our results should not be directly extrapolated to pediatric or geriatric populations. We also acknowledge that it is possible that toxicology screens in the clinical environment may have been more commonly performed in blacks than whites, as well as in men over women, which may have resulted in potential unintended bias. Finally, the external validity of our results should only be applied to similar hyperglycemic patients in whom a urine toxicology screen is performed. It is possible that individuals in whom urine toxicology is performed, based on clinical grounds in the intensive care unit or emergency room, may be different from those who did not have urine toxicology performed based on higher index of suspicion for substance abuse. However, despite the potential for overestimation of cocaine use in this population, there was no difference in the rates of hyperglycemic crisis in our population.

Notwithstanding these limitations, our results did not demonstrate a clear relationship between cocaine use and simultaneous development of hyperglycemic crisis. We recognize that our study cannot definitively conclude whether cocaine is an important independent risk factor or precipitating cause for hyperglycemic crisis, and that the role of routine toxicology screening in the evaluation of hyperglycemic crisis cannot be clearly defined based on the available data and literature. However, prospective studies investigating the etiology of hyperglycemic crisis, detailed patterns of drug use, including prospective testing of all relevant patients for cocaine use, and insulin self-administration around the time of admission for hyperglycemic crisis are needed to clearly define a possible causal relationship between cocaine and hyperglycemic crisis.

## Conclusions

We report no association between cocaine use and the simultaneous development of hyperglycemic crisis in patients admitted with hyperglycemia to an urban academic medical center. In addition, the severity of hyperglycemic crisis was not exacerbated by active cocaine use.

## Conflict of interest disclosures

None reported.

## Disclosures

Parts of this study were presented in abstract form as a poster at the 74th Scientific Sessions of the American Diabetes Association in San Francisco, California, 13–17 June 2014.

## Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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