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ORIGINAL ARTICLE

Predictors of acute gastrointestinal bleeding in diabetic ketoacidosis: a retrospective observational study in minority population

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Abstract

Background: Diabetic ketoacidosis (DKA) is a common acute complication of diabetes mellitus requiring aggressive medical management. We attempted to study the incidence and various clinical and laboratory variables associated with acute gastrointestinal bleeding (AGIB) and acute upper AGIB (AUGIB) in patients with DKA.
Methods: We conducted a retrospective chart review of all the patients admitted to our hospital with DKA between January 2010 and December 2015. We collected demographic, clinical, laboratory, endoscopy and hospitalization details using an electronic medical-record database. Patients were divided into two groups based on the occurrence of gastrointestinal bleeding.
Results: A total of 234 patients with DKA were admitted during this period, of which 27 (11.5%) patients had documented AGIB. The majority of patients had hematemesis (n=22, 9.4%) except two had rectal and three had occult bleeding. We did not notice any difference in age, gender and ethnicity distribution between the two groups. There was no difference in the serum levels of electrolytes, anion gap, pH and hemoglobin A1C between the two groups. However, patients with AGIB had significantly higher initial blood glucose levels (738 *vs* 613 mg/dL, p =0.014). There was also increased mortality (7.4% *vs* 4.8%) in patients with AGIB, but this did not reach statistical significance.
Conclusion: We conclude that higher initial serum blood glucose was associated with increased incidence of AGIB in patients admitted with DKA. We also noted increased in-patient mortality in patients with DKA who had AGIB, even though statistically insignificant. More aggressive measures to correct blood glucose levels may result in decreased incidence of AGIB, thereby reducing mortality during hospitalization in patients with DKA.

Key words: diabetic ketoacidosis, gastrointestinal bleeding, mortality

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Introduction

Diabetes mellitus is a worldwide pandemic with ever-increasing prevalence. The estimated prevalence in the United States is 29.1 million, which constitutes about 9.3% of the population [1]. Diabetic ketoacidosis (DKA) is a common indication for general and critical-care hospitalizations in this population [2,3]. DKA is one of the acute complications of uncontrolled diabetes mellitus and may present with a spectrum of gastrointestinal symptoms such as abdominal pain, nausea and vomiting [4]. Frequently, gastrointestinal bleeding is associated with DKA and is a common reason to seek in-patient gastroenterology evaluation. Gastrointestinal bleeding may be overt or occult at presentation [5]. Overt gastrointestinal bleeding can be frank hematemesis, coffee-ground emesis, melena or hematochezia.

We have identified a need to study the incidence of gastrointestinal bleeding, associated risk factors and the prognosis of such bleeding, as there are not many studies performed from this perspective. In this regard, we have attempted to evaluate the incidence of gastrointestinal bleeding in the setting of DKA. We hypothesized that demographic, clinical and laboratory variables may contribute to the gastrointestinal bleeding in this cohort. The study also was aimed to look at the endoscopic details and associated therapeutic interventions performed.

Methods

A retrospective chart review was conducted between January 2010 and December 2015. This study was approved by the Institutional Review Board at our institution, Bronx Lebanon Hospital Center, New York. We included all patients admitted with the diagnosis of DKA to our institution. Patient records were searched in the hospital's electronic medical-record database for discharge diagnosis carrying ICD 9 (250.10) and ICD 10 (E13.10) codes.

DKA is defined as elevated blood glucose, presence of ketones in blood or urine and metabolic acidosis accompanied by anion gap. The diagnosis and management of DKA were according to current critical-care protocols [6]. All individuals aged 18 years and above were included in the study. Baseline demographic data including age, gender and ethnicity were collected. Laboratory data that included electrolytes, renal function, anion gap and lactate levels were obtained at the admission and 24 hours after resuscitation. Hospitalization characteristics such as overall length of stay and critical-care length of stay, vasopressor use and requirement for mechanical ventilation that may contribute to in-patient morbidity were recorded. We also documented the all-cause mortality rate during that specific hospitalization.

Details about endoscopy and endoscopic interventions were obtained from ProVationMD, which is the hospital's electronic endoscopy database. All endoscopies were performed by one of the nine gastroenterologists at the hospital-based endoscopic center. All endoscopies were performed under monitored anesthesia care or general anesthesia delivered by a team of anesthesiologists and certified registered nurse anesthetists.

Based on the occurrence of gastrointestinal bleeding, study individuals were subdivided into two groups: those with or without gastrointestinal bleeding. Individuals with gastrointestinal bleeding were further subdivided into those with overt bleeding or those with occult bleeding. Occult bleeding is defined as a positive hemo-occult performed on stool samples obtained during a suspected gastrointestinal-bleeding episode. Overt bleeding was considered when the patient had frank hematemesis, coffee-ground emesis, melena or rectal bleeding.

A manual chart review was conducted by individual internal medicine physicians and endoscopic details were reviewed by gastroenterology faculty members. Data were analysed using JMP 12 software with standard statistical methods. Proportions were used to calculate incidence rates. For the association of two categorical variables, we used chi-square analysis; for association of one categorical and one continuous variable, we used *t*-tests; and, for the association of two continuous variables, we used Pearson's correlation. A *p*-value of less than 0.05 was considered statistically significant.

Results

Initial search results yielded a total of 234 patients who met the inclusion and exclusion criteria. Of the 234 DKA patients, 27 developed AGIB during their admission. Based on the number, the incidence of AGIB in the setting of DKA was 11.5%. The remaining 207 patients were included in the non-AGIB group. Patients with AGIB were further divided into patients with overt bleeding (n=24) and those with occult bleeding (n=3). The incidence of overt bleeding was 10.2% of the total patients with DKA. Among the patients with overt bleeding, 22 patients had acute upper gastrointestinal bleeding (AUGIB), reaching an incidence of 9.4%, while two patients had lower gastrointestinal bleeding with an incidence of 0.8% (Figure 1).

Demographic variables

The mean age of patients in the AGIB group was 54.5 years versus 52 years in the non-AGIB group (p =0.43). The proportion of male patients was 48% in the AGIB group versus 43.0% in the non-AGIB group (p =0.38). Gender and ethnicity did not play a significant role in the occurrence of bleeding (both p >0.05). There was no statistically significant difference in the prevalence of obesity and Charlson comorbidity index (CCI) between the two groups (Table 1).

Laboratory variables

The various laboratory variables studied included electrolytes, renal function, anion gap, blood glucose, pH and lactate levels

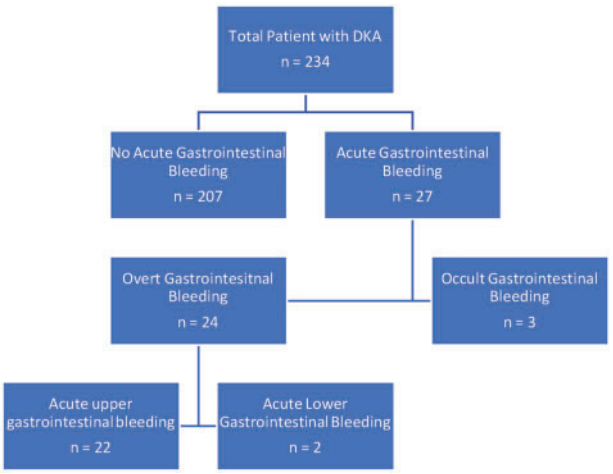

Figure 1. Initial search results of patients admitted with diabetic ketoacidosis (DKA) who had gastrointestinal bleeding during the study period.

Table 1. Demographic variables

	AGIB (*n*=27)	Non-AGIB (*n*=207)	*p*-value	AUGIB (*n*=22)	Non-AUGIB (*n*=212)	*p*-value
Gender,*n* (%)			0.38			0.55
Male	13 (48.1)	89 (43.0)		11 (50.0)	91 (42.9)	
Female	14 (51.9)	118 (57.0)		11 (50.0)	121 (57.1)	
Ethnicity, *n* (%)			0.056			0.19
Hispanic	17 (63.0)	90 (43.5)		13 (59.1)	94 (44.3)	
Non-Hispanic	10 (27.0)	117 (56.5)		9 (40.9)	118 (55.7)	
Mean age, years	54.5	52	0.43	50.5	52	0.65
BMI, *n* (%)			0.1			0.063
Obesity	6 (22.2)	79 (38.2)		4 (18.2)	81 (38.2)	
Normal	21 (77.8)	128 (61.8)		18 (81.8)	131 (61.8)	
Mean CCI	5	4	0.1	4.7	4	0.37

AGIB, acute gastrointestinal bleeding; AUGIB, acute upper gastrointestinal bleeding; BMI, body mass index; CCI, Charlson comorbidity index.

Table 2. Laboratory variables

	AGIB (*n*=27)	Non-AGIB (*n*=207)	*p*-value	AUGIB (*n*=22)	Non-AUGIB (*n*=212)	*p*-value
Mean pH	7.22	7.25	0.26	7.23	7.25	0.53
Mean anion gap (mmol/L)	26	25	0.51	26.6	24.8	0.41
Mean sodium (mEq/L)	133	131	0.34	133	131	0.21
Mean potassium (mEq/L)	4.9	5	0.44	4.7	5	0.22
Mean chloride (mEq/L)	92	91	0.4	91	91	0.83
Mean bicarbonate (mEq/L)	15.5	16.5	0.49	15.7	16.4	0.63
Mean BUN (mg/dL)	45	38	0.28	44	38	0.45
Mean serum creatinine (mg/dL)	2.57	2.16	0.36	2.4	2.2	0.64
Mean hemoglobin A1C (%)	11.1	11.72	0.3	10.7	11.8	0.092
Mean blood glucose (mg/dL)	738	613	0.014	721	618	0.063
Mean lactic acid (mmol/L)	4.64	3.46	0.056	4.31	3.52	0.25

AGIB, acute gastrointestinal bleeding; AUGIB, acute upper gastrointestinal bleeding; BUN, blood urea nitrogen.

Table 3. Endoscopic findings

AGIB group (*n*=10)	Non-AGIB group (*n*=4)
Esophagus (*n*=6)	Esophagus
Esophagitis	None
Scarring	
Varices	
Esophageal ulcers	
Stomach (*n*=2)	Stomach (*n*=1)
Gastric erythema	Gastric erosion
Duodenum (*n*=1)	Duodenum (*n*=1)
Duodenal bulb erythema	Duodenal ulcer
Normal endoscopy (*n*=1)	Normal endoscopy (*n*=2)

(Table 2). Blood urea nitrogen (BUN), creatinine and lactate may be altered in both gastrointestinal bleeding and DKA. We attempted to study the effects of aggressive resuscitation on the outcomes in patients with DKA. In this regard, we evaluated the change in electrolytes and metabolic markers after 24 hours of resuscitation. We classified the electrolytes/markers as low, normal or high at baseline. After 24 hours of resuscitation, these parameters could be low, normal or high. On a combination basis, this yielded nine combinations.

We have noted that the initial blood glucose levels (p =0.014) were higher in the AGIB group than in the non-AGIB group. Similar trends were noted for AUGIB, even though it did not reach statistical significance. We also noted that, in the majority of AUGIB patients (13 of 22 patients), lower admission bicarbonate levels were not corrected despite initial 24 hours of resuscitation (p =0.04) and remained in the acidotic range.

Endoscopic findings

Out of all the patients included in the study, 14 had endoscopy done, 10 patients in the AGIB group and four in the non-AGIB group. Only one patient needed therapeutic intervention to achieve hemostasis. In the AGIB group, endoscopic findings include esophageal lesions (esophagitis, esophageal ulceration, scarring and varices) in six patients, gastric erythema in two patients, duodenal bulb erosion in one patient and one had a normal endoscopy. In the non-AGIB group, two patients had normal endoscopy, one had gastric erosion and one had a duodenal ulcer. It was a non-bleeding clean-based ulcer that did not require therapeutic intervention (Table 3).

Hospitalization variables

The use of mechanical ventilation, use of vasopressors during hospitalization, length of stay including overall hospital length of stay and critical-care length of stay were studied in both groups (Table 4). Increased mortality was noted in DKA patients who had AGIB during the hospital course (7.4% in the AGIB group *vs* 4.8% in the non-AGIB group), although this did not reach statistical significance.

Table 4. Hospitalization variables

	AGIB (*n*=27)	Non-AGIB (*n*=207)	*p*-value	AUGIB (*n*=22)	Non-AUGIB (*n*=212)	*p*-value
Mean hospital length of stay, days	7.9	7.1	0.51	8	7.1	0.55
Mean intensive-care unit (ICU) length of stay, days	3.1	2.8	0.76	3.2	2.8	0.67
Use of mechanical ventilation, *n* (%)	2 (7.4)	21 (10.1)	0.65	1 (4.5)	22 (10.4)	0.38
Use of vasopressors, *n* (%)	2 (7.4)	13 (6.3)	0.82	1 (4.5)	14 (6.6)	0.71
Mortality, *n* (%)	2 (7.4)	10 (4.8)	0.57	1 (4.5)	11 (5.2)	0.9

Discussion

DKA represents a common complication of uncontrolled diabetes mellitus and invariably results in multiple hospitalizations. The Bronx borough represents an area in the United States with high rates of diabetes and complications [7]. Gastrointestinal symptomatology spectrum including bleeding that usually accompanies DKA is a common reason to seek gastroenterology consultation in our hospital. The study was primarily aimed to evaluate the association between gastrointestinal bleeding and diabetic ketoacidosis.

Gastrointestinal manifestations in uncontrolled diabetes mellitus may be due to gastric autonomic neuropathy, which may occur secondary to effects on intrinsic enteric nerves or extrinsic autonomic nerves, parasympathetic vagus nerves and sympathetic mesenteric innervation [8]. It has also been postulated that uncontrolled diabetes influences the functioning of interstitial cells of Cajal, which are essentially the pacemaker cells of the gut involved in the control of motility [9]. Metabolic derangements including ketonemia and acidosis that accompany DKA may be associated with acute gastric dilatation, which probably accounts for the gastrointestinal symptoms in this acute hyperglycemic state [10].

Although there have been few reports of gastrointestinal bleeding in DKA, to date, there is a paucity of studies in this area [11]. In our search, we have noted the research performed by Faigel *et al.* in 1996, in which an association between upper gastrointestinal bleeding and DKA was studied [5]. In their study, they concluded that the upper gastrointestinal hemorrhage correlated with blood glucose and creatinine levels. Also, the need for blood transfusions, increased critical-care admissions and the trend towards increased mortality were noted in patients with DKA who had upper gastrointestinal bleeding.

More than a decade has passed since the prior study was reported. We believe that, during this timeline, there have been advancements in the acute care of DKA, with more aggressive and better management practices. With this background, we have tried to study the incidence of overall gastrointestinal bleeding and upper gastrointestinal bleeding along with various demographic, laboratory and endoscopic findings, and morbidity and mortality parameters. More specifically, we wanted to look at how the management of underlying metabolic derangements affected the outcomes. To achieve this, we studied the outcomes in association with the changes in these metabolic markers in the first 24 hours. We believe that this is a novel idea and has never been studied before.

Our study notes an overall prevalence of 11.5% of gastrointestinal bleeding and 9.4% of upper gastrointestinal bleeding in DKA patients. The overall incidence of upper gastrointestinal bleeding seems to have been unchanged even with the passage of more than two decades since the last study [5]. Although, numerically, a 9.4% incidence of upper gastrointestinal bleeding appears smaller, considering the magnitude of admissions for DKA, this may translate into significant morbidity and mortality [12].

CCI is a novel way of measuring the magnitude of underlying co-morbid conditions [13]. To assess the differences in the baseline comorbidities in both, we have taken CCI as a measure and both groups seem to be similar. This is unique to our study and we conclude broadly that the findings in the study are not skewed by baseline patient co-morbid spectrum.

We have noted that initial blood glucose is associated with more bleeding. Acute gastric dilatation and altered esophageal motility may be related to higher blood sugars [14]. Also, there have been studies predicting adverse outcomes in patients with gastrointestinal bleeding when they had higher blood glucose levels [15]. Among the hospitalization characteristics, there has been no significant difference in the length of stay—both the overall and critical-care length of stay. Also, both the groups were similar with regard to the use of mechanical ventilation and vasopressors for hemodynamic support. We postulate that advances in critical-care monitoring and aggressive management practices may have resulted in these non-significant differences.

Interestingly, although not statistically significant, an overall mortality of 7.4% was noted in DKA patients with gastrointestinal bleeding. We feel that this number may be important clinically given the trend for increased mortality when bleeding complicates DKA and this calls for more aggressive care in this group. We do not think that this difference can be attributed to differences in baseline comorbidities given that both groups were similar with respect to their baseline CCI. This finding raises the question of the possibility of gastrointestinal bleeding being considered as a prognostic marker in DKA outcome. Also, possibly, even if the bleeding is not clinically significant and does not need emergent endoscopic intervention, still this should alert the treating physician to a more targeted aggressive management of metabolic parameters in this group.

Our study is not without limitations. Limitations include the overall small sample size and the few patients receiving endoscopic evaluation among those that had bleeding and the unavailability of data regarding the use of non-steroidal anti-inflammatory drugs (NSAIDS) and anticoagulants prior to hospital admission. Larger multi-center prospective studies in future may contribute to and confirm these findings.

Conflict of interest statement: none declared.

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