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Effect of diabetic ketoacidosis on the outcomes of ST-elevation myocardial infarction: An analysis of national inpatient sample

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Diabetes is a major risk factor for coronary artery disease worldwide. The incidence of CAD is known to be as high as 50% in diabetic patients [1,2]. It has been established that survival and immediate mortality after a myocardial infarction is affected by diabetes [3,4]. Complications such as cardiogenic shock, congestive heart failure, conduction abnormalities, and large anterior wall transmural infarcts are more common in the diabetic patient than non-diabetic patient [3]. Hyperglycemia with or without diabetes has also been shown to be independently associated with increased in-patient mortality and microvascular obstruction in ST-elevation myocardial infarction (STEMI) patients [5,6].

However, there is limited data on patients with STEMI and acute hyperglycemic state such as diabetic ketoacidosis (DKA). DKA is an acute complication of diabetes leading to significant metabolic derangements that can be fatal if not addressed. DKA is driven by insulin deficiency or resistance and increased counter-regulatory hormones (like glucagon, catecholamines) in an acute infectious/inflammatory state. With the advent of insulin, the incidence of DKA over the last century has decreased in hospitals. DKA is encountered in in-patient clinical practice and can also be seen concomitantly with a STEMI. The aim of this study is to improve our understanding of the factors influencing the outcomes in STEMI patients presenting with DKA in comparison to STEMI patients without DKA.

In this retrospective cohort study, we used the most updated 2016 National Inpatient Sample (NIS) database using the ICD 10 code for ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) both STEMI and DKA. Primary outcome of interest was in-hospital mortality. Secondary outcomes of interests were cardiogenic shock, cardiac arrest and acute kidney injury, length of stay and cost of care. Multivariate logistic regression was used to adjust for potential confounders including age, gender, race, socioeconomic status, diabetes, hypertension, smoking, alcohol use, chronic kidney disease, obesity, dyslipidemia, Charlson Comorbidity Index, hospital location, hospital region, teaching status, and hospital size. STATA/IC 15.1 Stata Corp LLC was used for analysis.

In the year 2016, the total number of hospitalizations with the primary diagnosis of STEMI was 152,385 of which 745 patients had a concomitant diagnosis of DKA. The mean age was 61.4 (59.4–63.3) yrs. in patients with DKA, and the mean age was 63 (62.8–63.2) yrs. in patients without DKA without any statistically significant difference ($p = 0.11$). Above 70% of patients was Caucasian in both groups. In DKA group there were more female (44% vs 30%; $p \leq 0.001$) and a greater number of patients had chronic kidney disease (26% vs. 12%; $p \leq 0.001$). Hypertension (57% vs. 47%; $p = 0.01$) and hyperlipidemia (61% vs. 53%; $p = 0.04$) were higher in patients without DKA [Table 1]. We observed a significant increase in mortality [Odds ratio (OR): 5.1 (3.2–8), p: <0.001], cardiac arrest [OR: 2.5 (1.6–4), p: <0.001], acute kidney injury [OR: 10 (6.7–15), p: <0.001], ICU stay [OR: 6.8 (2.6–7.3), p: <0.001] and cardiogenic shock [OR: 4.8(3.3–6.8), p: <0.001] in patients with DKA in comparison to patients without DKA. Length of stay [7.4 days (6–8.8) in STEMI with DKA group vs 4 days (3.9–4.1) in STEMI without DKA group; p: <0.001] and cost of care (185,649 in STEMI with DKA vs 107,002 in STEMI without DKA, p: <0.001) were also higher in patients of STEMI with DKA [Table 2].

The NIS database is the largest inpatient database representative of >95% of the US population. Utilizing this database, we showed the

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Table 1
Baseline characteristics.

Baseline demographics, comorbidities in patients admitted with STEMI ($n = 152,385$) with and without diabetic ketoacidosis (DKA)			
	STEMI with DKA ($n = 745$)	STEMI without DKA ($n = 151,640$)	p value
Mean age	61.4 (59.4–63.3)	63 (62.8–63.2)	0.11
Female gender (%)	44%	30%	<0.001
Race (%) 0.01			
Caucasian	72%	77.2%	
Black	7.2%	8.3%	
Hispanic	13.7%	7.8%	
Hypertension	47%	57%	0.01
Diabetes	25.5%%	30%	0.2
Smoker	16%	20.8	0.16
Dyslipidemia	53%	61%	0.04
Obesity	20%	15%	0.08
CKD	26%	12%	<0.001
Length of stay	7.4 (6–8.8)	4 (3.9–4.1)	<0.001
Cost of care	185,649	107,002	<0.001
Median household income in dollars (%) 0.45			
1–39,999	33.33%	28%	
40,000–50,999	26.5%	27%	
51,000–65,999	20.4%	25%	
66,000 and more	19.7%	20%	
Hospital location/teaching 0.15			
Rural	7.4%	5.7%	
Urban-nonteaching	20.8%	27.4%	
Urban teaching	71.8%	67%	
Insurance <0.001			
Medicare	48.3%	43.6%	
Medicaid	20.1%	10.5%	
Private including HMO	20.8%	35.6%	
Region of hospital 0.90			
North-east	18.8%	16.5%	
Mid-west	23.5%	23.7%	
South	38.3%	40%	
West	19.5%	19.8%	
Hospital bed size 0.70			
Small	11.4%	13.1%	
Medium	27.5%	29%	
Large	61%	57.8%	

CKD: chronic kidney disease.

following significant findings: 1) Patient characteristic such as sex, hypertension and chronic kidney disease were significantly different in DKA patients compared with non-DKA patients (p-value <0.05). 2) Incidence of DKA in STEMI patients was 0.5%. 3) DKA in STEMI patients was associated with increased mortality (OR 5.1, $p < 0.001$), cardiogenic shock (OR 4.8, $p < 0.001$), cardiac arrest (OR 2.5, $p < 0.001$), and acute kidney injury (OR 10, $p < 0.001$). 4) DKA in STEMI patients was associated with increased ICU stay (OR 6.8, $p < 0.001$), length of stay and cost of care.

The baseline characteristics revealed more women in the DKA group than in the non-DKA ($p < 0.001$), which could be explained by the higher prevalence of DKA in women in the general population. There were fewer patients with a history of hypertension in the DKA group.

Table 2
In-hospital outcomes for patients admitted with STEMI ($n = 152,385$) with and without diabetic ketoacidosis (DKA).

Outcomes	Odds ratio (OR)	p value
Mortality	OR: 5.1 (3.2–8)	<0.001
Cardiac arrest	OR: 2.5 (1.6–4)	<0.001
Acute kidney injury	OR: 10 (6.7–15)	<0.001
ICU stay	OR: 6.8 (2.6–7.3)	<0.001
Cardiogenic shock	OR: 4.8 (3.3–6.8)	<0.001

CKD was two times more common in the DKA group compared to the non-DKA group. CKD leads to an immune-compromised state and is at high risk of infections. Acute infectious and inflammatory states often are the triggers for DKA.

DKA typically occurs in states of physiological stress such as in patients with sepsis, multiple trauma, burn injuries, or even in acute myocardial infarction (AMI). During DKA the release of counter-regulatory hormones, pro-inflammatory markers, and development of insulin resistance can lead to activation of reactive oxygen species, prothrombotic state formation and coronary vascular inflammation [7]. The eventual fatal outcome often times is an AMI. Studies have shown that AMI patients with a hyperglycemic state are associated with plaque instability, and increased infarct size [8]. At a molecular level increase in glucose activates protein kinase C and nuclear-kB pathway, which then leads to expression of more adhesive molecules on the vascular surface leading to prothrombotic state [9,10]. Insulin typically activates nitric oxide synthase, which inhibits platelet aggregation, whereas in a DKA state the lack of insulin sets the stage for a fatal event like STEMI [11].

In a recent trial by Liao et al. showed that patients presenting to the ER with a higher glycemic gap (difference patient's admission glucose and HbA1-c average derived glucose) experienced major adverse cardiovascular events [12]. Similarly, Issa et al. showed worse cardiovascular outcomes in NSTEMI patients presenting with concomitant DKA/hyperosmolar hyperglycemic state (HHS) [13].

There may be a lack of DKA patients in large prospective clinical trials due to their inherently "sick" presentation with other major medical comorbidities. Hyperglycemia, in general, is associated with increased mortality with an odds ratio or >4 and 10% increase in mortality if blood glucose levels are >300 [14]. DKA is typically associated independently with increased mortality, and multiple organ failure if undiagnosed and untreated promptly. When combined with another fatal event like a STEMI, our data seems to suggest across the board of increased poor outcomes in terms of overall mortality, cardiac arrest, cardiogenic shock, and acute kidney injury.

Our study also showed that length of stay and increased cost of admission were seen in DKA patients with STEMI. This same phenomenon of increased length of stay has previously been reported in DKA with acute ischemic stroke patients [15].

As this is a retrospective observational study, it does have some limitations. The NIS database does not separate the number of encounters from each individual patient. So there is a chance to capture readmissions of a single patient multiple times. We are lacking patient-level data such as adherence to medications, duration of disease, extent of myocardial involvement, and other lab parameters. There also exists bias secondary to not accounting for all confounders, despite trying to account and performing multivariate analysis for as many variables as possible. Finally, this is a retrospective study and cannot draw any causal relationships but can strongly point towards major associations.

The generalizability of the NIS database to the US population is a relatively well researched and validated tool. The reaching implications of this study are to recognize DKA in STEMI patients early when seen and to swiftly initiate treatment of DKA along with discussion with the interventional cardiologist regarding antiplatelet therapy and possible revascularization strategy.

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