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 significantly 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].

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 ≤ 0.001) and a greater number of patients had chronic kidney disease (26% vs. 12%; p ≤ 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) 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
following significant findings: 1) Patient characteristic such as sex, hyper- 
pertension and chronic kidney disease were significantly different in 
DKA patients compared with non-DKA patients (p-value <0.05). 2) Inci- 
dence 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 1
Baseline characteristics.

|                        | 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 (%)               |                          |                                 |        |
| 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           | 185,640                  | 107,002                         | <0.001 |

Median household income in dollars (%) 0.45
1–39,999 33.3% 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.

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 pa- 
patients with sepsis, multiple trauma, burn injuries, or even in acute myo- 
cardial infarction (AMI). During DKA the release of counter-regulatory 
hormones, pro-inflammatory markers, and development of insulin res- 
sistance can lead to activation of reactive oxygen species, prothrombotic 
state formation and coronary vascular inflammation [7]. The eventual 
fatal outcome often times is an AML. Studies have shown that AMI pa- 
patients with a hyperglycemic state are associated with plaque instability, 
and increased infarct size [8]. At a molecular level increase in glucose ac- 
tivates 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 syn- 
these, 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 cardiovascu- 
lar 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 tri- 
als 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 indepen- 
dently with increased mortality, and multiple organ failure if undiag- 
nosed 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 lim- 
itations. 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 dis- 
ease, 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 can- 
not 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 implica- 
tions of this study are to recognize DKA in STEMI patients early 
when seen and to swiftly initiate treatment of DKA along with dis- 
cussion with the interventional cardiologist regarding antiplatelet 
therapy and possible revascularization strategy.

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 |

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