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Association of hyperglycemia with in-hospital mortality and morbidity in Libyan patients with diabetes and acute coronary syndromes --Manuscript Draft--

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Abstract:	<p>Background. Hyperglycemia on admission and during hospital stay is a well-established predictor of short-term and long-term mortality in patients with acute myocardial infarction. This study investigated the impact of admission and in-hospital hyperglycemia on the morbidity and mortality of Libyan patients admitted with acute coronary syndromes (acute myocardial infarction and unstable angina).</p> <p>Patients and Methods. In this retrospective study, the records of patients admitted with acute coronary syndrome to the 7th of October Hospital (Benghazi, Libya) between January 2011 and December 2011 were reviewed. The level of blood glucose at admission, and the average blood glucose during hospital stay were recorded to determine their effects on in-hospital complications (cardiogenic shock, acute heart failure, arrhythmias, and/or heart block) and mortality.</p> <p>Results. During the study period, 121 patients with diabetes were admitted with acute coronary syndrome. The mortality rate in patients with diabetes and acute coronary syndrome was 12.4%. Patients with a mean glycemia > 200 mg/dL had a higher in-hospital mortality and higher rate of complications than those with a mean glycemia ≤ 200 mg/dL (27.5% vs. 2.6%, $P < 0.001$ and 19.7% vs. 45.5%, $P = 0.004$). There was no difference in in-hospital mortality between patients with a glucose level at admission ≤ 140 mg/dL and those admitted with a glucose level > 140 mg/dL (6.9% vs. 14.3%, $P = 0.295$), but the rate of complications was higher in the latter group (34.1% vs. 13.8%, $P = 0.036$). Patients with admission glucose levels > 140 mg/dL also had a higher rate of complications at presentation (26.4% vs. 6.9%, $P = 0.027$).</p> <p>Conclusions. In patients with diabetes and acute coronary syndrome, hyperglycemia during hospitalization predicted a worse outcome in terms of the rates of in-hospital complications and in-hospital mortality. Hyperglycemia at the time of admission was</p>

	also associated with higher rate of complications particularly at the time of presentation.
Response to Reviewers:	Reviewer #1: <ul style="list-style-type: none">- All reference numbers within the text are now changed to superscript- ref 6 was missing from the introduction and has been added.-HbA1c has been corrected and defined as Glycosylated hemoglobin.- ABG was changed to admission blood glucose.- Legends added to tables.- month of publication has been deleted from ref 4, 5, 21 and 22.- inconsistency in page numbering in references has been corrected.

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Editor-in-Chief
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Dear Dr. Editorian:

I am pleased to submit an original article entitled “**Association of hyperglycemia in-hospital mortality and morbidity in Libyan patients with diabetes and acute coronary syndromes**” by Sufyan Benamer, Imhemed Eljazwi, Rima Mohamed, Heba Masoud, Mussa Tuwati and Abdulwahab Elbarsha for consideration for publication in the **Oman Medical Journal**.

The paper studies the impact of hyperglycemia on the mortality and morbidity of diabetic patients admitted with acute coronary syndrome, a commonly encountered situation in everyday hospital practice. The paper shows that hyperglycemia at admission and during hospital, stay has an adverse impact on the outcome of such patients. We think that the results are of interest to a wide category of practitioners including hospital physicians, cardiologists, intensivists, diabetologists and endocrinologists.

This manuscript has not been published and has not been submitted or considered for publication elsewhere. We have no conflicts of interest to disclose. All authors have contributed significantly to the manuscript and all of them are in agreement with the content of the manuscript.

No ethical approval is needed for this manuscript.

Thank you for your consideration

Sincerely,

Abdulwahab Elbarsha

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Title Page

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ABSTRACT

Background. Hyperglycemia on admission and during hospital stay is a well-established predictor of short-term and long-term mortality in patients with acute myocardial infarction. This study investigated the impact of admission and in-hospital hyperglycemia on the morbidity and mortality of Libyan patients admitted with acute coronary syndromes (acute myocardial infarction and unstable angina).

Patients and Methods. In this retrospective study, the records of patients admitted with acute coronary syndrome to the 7th of October Hospital (Benghazi, Libya) between January 2011 and December 2011 were reviewed. The level of blood glucose at admission, and the average blood glucose during hospital stay were recorded to determine their effects on in-hospital complications (cardiogenic shock, acute heart failure, arrhythmias, and/or heart block) and mortality.

Results. During the study period, 121 patients with diabetes were admitted with acute coronary syndrome. The mortality rate in patients with diabetes and acute coronary syndrome was 12.4%. Patients with a mean glycemia > 200 mg/dL had a higher in-hospital mortality and higher rate of complications than those with a mean glycemia ≤ 200 mg/dL (27.5% vs. 2.6%, $P < 0.001$ and 19.7% vs. 45.5%, $P = 0.004$). There was no difference in in-hospital mortality between patients with a glucose level at admission ≤ 140 mg/dL and those admitted with a glucose level > 140 mg/dL (6.9% vs. 14.3%, $P = 0.295$), but the rate of complications was higher in the latter group (34.1% vs. 13.8%, $P = 0.036$). Patients with admission glucose levels > 140 mg/dL also had a higher rate of complications at presentation (26.4% vs. 6.9%, $P = 0.027$).

Conclusions. In patients with diabetes and acute coronary syndrome, hyperglycemia during hospitalization predicted a worse outcome in terms of the rates of in-hospital complications and in-hospital mortality. Hyperglycemia at the time of admission was also associated with higher rate of complications particularly at the time of presentation.

Keywords: acute coronary syndrome, acute myocardial infarction, unstable angina, diabetes, glucose.

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide ^[1]. In 2008, 17.3 million people died from this disease; 7.3 million of those deaths were due to acute myocardial infarction (AMI) ^[1]. Diabetes mellitus (DM) is a well-known risk factor for coronary artery disease ^[2]. Poor glycemic control can lead to endothelial injury, and thus to coronary artery disease and myocardial infarction ^[2]. In both diabetic and non-diabetic patients, hyperglycemia is a common concomitant finding in patients with acute myocardial infarction. Epidemiological studies showed that more than half of patients with AMI had hyperglycemia at the time of hospital admission ^[3].

Previous studies from different populations demonstrated that hyperglycemia at admission and during hospital stay was associated with poorer outcomes in both diabetics and non-diabetics ^[4,5].

Hyperglycemia has been linked to increased morbidity, serious complications such as congestive heart failure (CHF) and cardiogenic shock, and mortality ^[6-14].

However, evidence of a direct correlation between elevated blood glucose and outcomes, including AMI, is lacking ^[9, 10, 12-14].

In this study, we retrospectively examined the relationship between hyperglycemia at the time of hospital admission and during hospital stay ACS and diabetes.

PATIENTS AND METHODS

The medical records of patients admitted with acute coronary syndrome to the 7th of October Hospital (Benghazi, Libya) between January 2011 and December 2011 were reviewed retrospectively. Demographic data and data on the presence or absence of diabetes, hypertension, tobacco smoking, and history of previous myocardial infarction were collected from the patients' medical records. Details of treatment, particularly thrombolytic and anti-platelet therapies, were noted.

The level of blood glucose at admission and the average blood glucose during hospital stay were recorded to determine their effect on in-hospital mortality and complications. The mean in-hospital blood glucose was only calculated for those patients for whom at least three blood glucose measurements were available.

Patients were categorized into two groups according to their admission glucose; those with admission glucose of ≤ 140 mg/dl and those with admission glucose of >140 mg/dL. Similarly, patients were also categorized into those whose mean blood glucose is ≤ 200 mg/dL and those with mean blood glucose of >200 mg/dL.

Differences in mortality and rates of complications were determined between each set of groups. Recorded complications included cardiogenic shock, acute heart failure, arrhythmias, and/or heart block.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0. Discrete variables were expressed as numbers and percentages, and continuous variables as the mean \pm standard deviation (SD).

Differences between categorical values were analyzed using the χ^2 test while student t-test was used for continuous values. *P* values < 0.05 were considered statistically significant.

RESULTS

During the study period, a total of 121 patients with diabetes, 4 with type 1 and 117 with type 2, were admitted with acute coronary syndrome (ACS).

AMI was the reason for admission in 71 (58.7%) patients, and unstable angina (UA) in the remaining 50 patients.

The overall in-hospital mortality rate was 12.4%. Mortality was higher in those with AMI than in those with UA, but the difference was not significant (16.9% vs. 6%, $P = 0.07$). Complications (cardiogenic shock, acute heart failure, arrhythmias, and/or heart blocks) occurred in 35 (28.9%) patients during their hospitalization.

Admission blood glucose was noted in the records of 120 patients out of the 121 patients who were admitted with ACS.

Table 1 shows the background characteristics of the 120 study patients categorized according to their blood glucose levels at admission. There was no difference in in-hospital mortality between patients with an admission glucose level ≤ 140 mg/dL and those with an admission glucose level > 140 mg/dL (6.9% vs. 14.3%, $P = 0.295$). Patients with an admission glucose level > 140 mg/dL have higher rate of complications at time of their presentation (26.4% vs. 6.9%, $P = 0.027$) as well as higher rate of overall complications occurring during their hospital stay (34.1% vs. 13.8%, $P = 0.036$).

Data from at least three measurements of blood glucose were available for 116 patients. Seventy six (65.5%) of these patients had an average blood glucose of ≤ 200 mg/dL and the remaining 40 (34.5%) had an average blood glucose of > 200 mg/dL.

Table 2 shows the background characteristics of the 116 patients with respect to their average blood glucose level. Those with a mean glycemia > 200 mg/dL had a higher in-hospital mortality (27.5% vs. 2.6%, $P < 0.001$) and a higher overall rate of in-hospital complications (19.7% vs. 45.5%, $P = 0.004$) than those with a mean glycemia \leq 200 mg/dL.

DISCUSSION

Several previous studies have shown that blood glucose levels predict the outcome of patients with diabetes and ACS [7–14].

Most of these studies relied on the first admission blood glucose level as a predictor of outcome [1, 7, 8, 15], whereas others used fasting blood glucose [15–17] or average glucose levels during the period of admission [18,19].

However, there is no well-accepted definition of hyperglycemia as different studies used different glucose levels to define hyperglycemia in this setting.

Several studies have suggested that blood glucose levels between 110 mg/dL and ≥ 200 mg/dL are associated with adverse outcomes [6]. In the American Heart Association Scientific Statement on Hyperglycemia and Acute Coronary Syndrome, hyperglycemia was defined as a blood glucose level > 140 mg/dL at any time during hospitalization [20]. However, the relationship between glycemic status and outcome may vary depending on the diabetic status of the patient. In non-diabetic patients, the mortality rate increases with blood glucose > 120 mg/dL, while in diabetic patients, a blood glucose > 200 mg/dL is associated with a poor outcome [6, 20].

In a large cohort study, Kosiborod et al. evaluated the relationship between blood glucose at admission, classified in five different groups (≤ 110 , > 110 –140, > 140 –170, > 170 –240, > 240 mg/dL), and patients with AMI [6]. They found that both short- and long-term mortality increased linearly with elevated admission glucose level. In patients with established DM, 30-day mortality increased from 10% to 39% and 1-year mortality from 22% to 55% as the blood glucose level at admission increased within a

range of 110–240 mg/dL [6]. However, their measurements consisted of only a single value at admission rather than hyperglycemia during the entire period of hospitalization.

In a large multicenter study from Oman, severe admission hyperglycemia, defined as blood glucose ≥ 200 mg/dL, was associated with increased in-hospital mortality among those without previously diagnosed diabetes but not among those with established diabetes [21].

Despite the differences in blood glucose cut-off points used by different studies, most of these studies consistently reported a high mortality rate and a high rate of cardiac complications, including CHF, malignant arrhythmia, and cardiogenic shock [6–14].

Glycosylated hemoglobin (HbA1c) have also been studied as a possible predictor of outcome in patients with ACS. Unlike blood glucose levels, studies of HbA1c yielded conflicting results. A study by Chan et al in patients with diabetes and ACS suggested that HbA1c levels are not associated in short-term (up to 6 months) outcomes [22].

In our study we assessed both the first admission blood glucose level as well as the mean glycemia during hospitalization using the cut-offs of 140 mg/dL and 200 mg/dL respectively.

We found no statistically significant difference in mortality rate between those who have an admission blood glucose of < 140 mg/dL and those with admission blood glucose of >140 mg/dL. However, mortality rates were higher among those with higher average blood glucose during hospitalization (>200 mg/dL).

There are many explanations for the lack of an effect of admission blood glucose on mortality in our study. First, other studies concluded similar results and suggested that it is the fasting blood glucose and not the random blood glucose taken at the time of admission predicts the mortality in ACS [19, 23].

Because of the retrospective nature of our study, we cannot verify the fasting status of our patients at the time of admission. Second, this lack of effect could also be attributed to the smaller number of those presenting with a blood glucose of less than 140 mg/dL (n=29) compared with those with levels > 140 mg/dL (n=91). However, both admission blood glucose and average blood glucose during hospitalization were associated with higher rate of complications both at the time of admission as well as during the hospitalization.

There are several mechanisms by which hyperglycemia may exacerbate myocardial damage and worsens the prognosis in patients with ACS. First, hyperglycemia induce oxidative stress by production of free radicals, which lead to myocardial cellular injury [24].

Hyperglycemia has also been shown to affect cardiac contractility and reduce both end-diastolic volume and stroke volume by promoting osmotic diuresis and lowering the circulating volume [25, 26].

Our patient population is slightly different from those in previous published studies, reflecting the type of patients treated in an under-resourced setting. First, there is no cardiac catheterization service in the study hospital meaning that all patients were treated either by thrombolytic therapy or anticoagulants.

Second, all our patients were treated by subcutaneous insulin sliding scale protocols instead of intravenous insulin infusion. However most patients (65%) achieved good control of blood glucose (<200 mg/dL) during the hospitalization.

CONCLUSION

Our study showed that hyperglycemia during hospital stay is accompanied by a worse outcome in terms of in-hospital mortality and rate of in-hospital complications in patients with diabetes and ACS. Hyperglycemia at admission was also associated with a higher rate of complications, particularly at the time of presentation.

Table 1: Characteristics of patients with diabetes and acute coronary syndrome according to their blood glucose level at admission.

	Admission glucose \leq 140 mg/dL	Admission glucose $>$ 140 mg/dL	p value
Number of patients (%)	29 (24.2%)	91(75.8%)	
Men	17 (58.6%)	49 (53.8%)	0.653
Age*	59 \pm 9	61 \pm 11	0.408
Hypertension	23 (79.3%)	51 (56%)	0.025
Smoking	5 (17.2%)	19 (20.9%)	0.670
History of previous MI	8 (27.6%)	11 (12.1%)	0.046
Past history of CAD	11 (37.9%)	40 (44%)	0.568
Mean Systolic BP*	150 \pm 31	145 \pm 34	0.501
Mean Diastolic BP*	86 \pm 16	86 \pm 19	0.978
Myocardial infarction	15 (51.7%)	55 (60.4%)	0.407
Thrombolysis	10 (34.5%)	29 (31.9%)	0.793
Anti-platelets	29 (100%)	88 (96.7%)	0.322

* mean \pm SD, BP: blood pressure, CAD: coronary artery disease, MI: myocardial infarction

Table 2: Characteristics of the patients with diabetes and acute coronary syndrome according to the mean glycemia level.

	Mean glycemia of ≤ 200 mg/dL	Mean glycemia of > 200 mg/dL	p value
Number of patients (%)	76(65.5%)	40(34.5%)	
Men	48(63.2%)	16(40%)	0.017
Age*	59 \pm 10	62 \pm 11	0.128
Hypertension	49(64.5%)	25(62.5%)	0.833
Smoking	17(22.4%)	5(12.5%)	0.198
History of previous MI	17(22.4%)	2(5%)	0.016
Past history of CAD	34(44.7%)	15(37.5%)	0.453
Mean Systolic BP*	143 \pm 45	151 \pm 29	0.223
Mean Diastolic BP*	85 \pm 21	90 \pm 13	0.171
Myocardial infarction	33(43.4%)	17(42.5%)	0.924
Thrombolysis	24(31.6%)	14(35%)	0.709
Anti-platelets	76(100%)	37(92.5%)	0.016

* mean \pm SD, BP: blood pressure, CAD: coronary artery disease, MI: myocardial infarction

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