Characteristics, management, and in-hospital outcomes of diabetic acute coronary syndrome patients in Oman

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ABSTRACT

الأهداف: دراسة بين مرضى السكري وغيرهم من المصابين بالأمراض الحادة للشرايين التاجية (ACS) من ناحية خصائص المرض السريرية، وطرق العلاج ونتائجه في سلطنة عمان.

الطريقة: أجري تحليل بيانات 1583 مريض تم تنويمهم في مستشفيات سلطنة عمان خلال الفترة من 8 مايو حتى 6 يونيو 2006م و 29 يناير إلى 29 يونيو 2007م كجزء من السجّل الخليجي للأمراض الحادة للشرايين التاجية RACE. يعد السجّل الخليجي للأمراض الحادة للشرايين التاجية سجل مستقبلي، يضم مجموعة من الجنسيات من مجموعة المراكز الطبية المعنية بالأمراض الحادة للشرايين التاجية. تم تقسيم المرضى إلى مجموعة مصابة بالسكري وأخرى غير مصابة.

النتائج: في هذه الدراسة، بلغ المرضى المصابين بالسكري 588 (37%) مريض، كان متوسط أعمارهم 59 عام واشتمل البحث على نساء مصابات بمرض بالسكري أكثر من الرجال (43% مقابل 33%) $p<0.001$. كان مرضى السكري معرضين أكثر للإصابة بالذبحة الصدرية الغير مستقرة (55% مقابل 44%) $p<0.001$ وأقل إصابة بالنوبة القلبية (20% مقابل 27%) $p=0.001$. تلقت المجموعتان على نفس النسبة من الأدوية المذيبة للجلطة وقسطرة القلب، لكن تلقى مرضى السكري على نسبة أعلى من الأدوية المضادة للجلايكوبروتين IIb/IIIa وتلك المضادة للإنزيم المحول للانجيوتنسين. بالإضافة إلى ذلك، أصيب مرضى السكري أكثر من غيرهم بتكرار الذبحة الصدرية (12% مقابل 8%) $p=0.043$، هبوط القلب (29% مقابل 23%) $p=0.009$ وصدمة القلب (7.5% مقابل 4.6%) $p=0.018$ وكان احتياجهم لجهاز التنفس الصناعي (7.3% مقابل 4.1%) $p=0.006$. عند التعديل مع العمر والجنس أن الإصابة بالسكري عامل خطورة مستقل لوفيات مرضى الأمراض الحادة للشرايين التاجية أثناء مكوثهم في المستشفى (adjusted OR, 1.68; 95% CI, 1.02–2.77; $p=0.042$).

خاتمة: أن مرضى السكري المصابون بالأمراض الحادة للشرايين التاجية لهم خصائص سريرية مختلفة ونتائج أسوأ من غيرهم. أنّ نمط العلاج الحالي غير كاف لمقاومة التأثيرات السلبية للمرض وهناك حاجة لاستخدام علاج أكثر فاعلية ومبني على الدليل العلمي لهذه الفئة من المرضى.

Objectives: To determine clinical characteristics, management, and in-hospital outcomes of diabetic and non-diabetic patients admitted with acute coronary syndrome (ACS) in Oman.

Methods: Data were analyzed from 1583 consecutive patients admitted to various hospitals in Oman with ACS from May 8 to June 6, 2006, and from January 29 to June 29, 2007, as part of the Gulf RACE (Registry of Acute Coronary Events). The ACS patients were stratified into those with and without diabetes mellitus.

Results: In this study, 588 (37%) patients were diabetic with a mean age of 59 years and included more female than male diabetics (43% versus 33%; $p<0.001$). Diabetic patients were more likely to present with unstable angina (55% versus 44%; $p<0.001$) and less likely to present with ST elevation myocardial infarction (20% versus 27%; $p=0.001$). Both groups received ACS treatment equally; however, diabetic patients were more likely to be treated with glycoprotein IIb/IIIa antagonists and angiotensin-converting enzyme inhibitors or receptor blockers. Diabetic patients experienced more recurrent ischemia (12% versus 8%; $p=0.043$), heart failure (29% versus 23%; $p=0.009$), cardiogenic shock (7.5% versus 4.6%; $p=0.018$), and ventilator requirement (7.3% versus 4.1%; $p=0.006$). When adjusted for age and gender, diabetes status was an independent risk factor of in-hospital mortality in ACS patients (adjusted odd ratio, 1.68; 95% confidence interval, 1.02–2.77; $p=0.042$).

Conclusions: Diabetic ACS patients have different clinical characteristics and poorer outcomes. Present treatment strategies are not sufficient to counter the adverse impact of diabetes. More effective and evidence-based therapeutic strategies should be identified and used in diabetic ACS patients.

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It is well known that diabetes mellitus is associated with an increased risk of cardiovascular morbidity and mortality. Diabetes is considered a coronary risk equivalent for future myocardial infarction, and cardiovascular death.[1] In addition to being an independent risk factor for coronary artery disease, diabetes influences outcomes following acute coronary syndrome (ACS). Among patients with ACS, diabetes mellitus is associated with poorer outcome and higher mortality rates.[2-4] The Global Registry of Acute Coronary Events (GRACE) revealed that in-hospital case fatality rate was twice higher among diabetic ACS patients in comparison to non-diabetic patients.[3] Furthermore, hyperglycemia in patients admitted for ACS is common and is associated with increased adverse outcomes in both diabetic, and non-diabetic populations.[5-8] The burden of diabetes mellitus in Middle Eastern countries is high.[9] There are no studies from the Middle East comparing the various outcomes of ACS in patients with and without diabetes mellitus. The aim of this study was to identify clinical characteristics, management, and various in-hospital outcomes of ACS in diabetic, and non-diabetic patients from Oman.

Methods. In this study, a prospective registry of consecutive ACS patients [Gulf Registry of Acute Coronary Events (RACE)] with and without diabetes (n=1583) were evaluated. The Gulf RACE was a prospective, multinational multicenter registry of consecutive patients above 18 years of age hospitalized with the final diagnosis of ACS from various hospitals in 6 Middle Eastern countries. There were no exclusion criteria. Recruitment in the pilot phase started from May 8 to June 6, 2006. Enrollment in the next phase of the registry started on January 29, and continued for 5 months until June 29, 2007. The present study included patients from the registry admitted to various hospitals in Oman during this period. The methods of the multinational Gulf RACE have already been described previously.[10] The patients were stratified into ACS with and without diabetes mellitus. Diabetes was defined as a known history of type 1 or type 2 diabetes mellitus treated with diet, oral hypoglycemic agents, or insulin. Demographic and other baseline clinical characteristics of the patients along with in-hospital management were evaluated. Outcome parameters evaluated during the hospital stay included in-hospital mortality, recurrent ischemia/re-infarction, heart failure, cardiogenic shock, major bleed, stroke and ventilator requirement. Institutional review board approval was obtained in all participating countries.

Statistical analysis. Descriptive statistics were used to describe the data. For categorical variables, frequencies, and percentages were reported. Differences between groups were analyzed using Pearson's x^2 tests (or Fisher's exact tests for cells less than 5). For continuous variables, means and standard deviations were presented and analyses were conducted using Student's t-test. To obtain age- and gender-adjusted in-hospital mortality, the analysis was performed using multivariable logistic regression and the results were presented as odds ratio (OR) with the associated 95% confidence interval. A priori two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 10.1 (STATA Corporation, College Station, TX, USA).

Results. A total of 1583 patients admitted with ACS were enrolled in the study. **Table 1** shows the

Table 1 - Patient baseline characteristics (n=1583).

Characteristic	DM (n=588)		Non-DM (n=995)		*P*-value
Age, mean±SD, years	59±11		59±14		0.831
Female	264	(43.0)	346	(57.0)	<0.001
Male	324	(33.0)	649	(67.0)	<0.001
Body mass index, mean± SD, kg/m^2	28±5		26±5		<0.001
Hypertension	406	(69.0)	430	(43.2)	<0.001
Hyperlipidemia	283	(48.1)	267	(27.7)	<0.001
Current smoker	73	(12.4)	205	(20.6)	<0.001
Family history of CAD	44	(7.5)	77	(7.7)	0.856
Prior Angina	322	(54.8)	442	(44.4)	<0.001
Past MI	108	(18.4)	180	(18.1)	0.897
Past PCI	50	(8.5)	68	(6.8)	0.220
Past CABG	48	(8.2)	60	(6.0)	0.105
Aspirin use	333	(57.0)	419	(42.1)	<0.001
COPD	28	(4.8)	49	(4.9)	0.884
Stroke	30	(5.1)	25	(2.5)	0.007
Dialysis	18	(3.1)	9	(0.9)	0.001
PVD	20	(3.4)	14	(1.4)	0.008
Ischemic chest pain	394	(67.0)	763	(76.7)	<0.001
Atypical chest pain	42	(7.3)	66	(6.6)	0.606
Dyspnea	114	(19.4)	103	(10.3)	<0.001
ST elevation	119	(20.2)	273	(27.4)	0.001
ST depression	221	(37.6)	312	(31.4)	0.011
LBBB	25	(4.3)	47	(4.7)	0.663
Other	195	(33.2)	334	(33.5)	0.887
Normal	27	(4.6)	29	(2.9)	0.080
Unstable angina	322	(54.7)	474	(47.6)	0.007
Non-STEMI	146	(24.8)	242	(24.3)	0.829
STEMI	117	(20.0)	271	(27.2)	0.001
LBBB MI	3	(0.5)	7	(0.7)	0.753

DM - diabetes mellitus, SD - Standard deviation, CAD - coronary artery disease, MI - myocardial infarction, PCI - percutaneous coronary intervention, CABG – coronary artery bypass surgery, COPD - chronic obstructive pulmonary disease, PVD - peripheral vascular disease, LBBB - left bundle branch block, STEMI - ST-elevation myocardial infarction, percents are column percentages. All values n (%) unless specified.

demographic and baseline clinical characteristics of the patients. In this study, 37% of the patients were diabetic while 63% were non-diabetic with no significant differences in age between the 2 groups. There were significantly more diabetics females than males. Diabetic patients were associated more with angina, hypertension, hyperlipidemia, higher body mass index (BMI), and aspirin uses but less likely to be associated with smoking. Diabetic patients were also more likely to have a prior diagnosis of peripheral vascular disease, dialysis, and history of stroke. Diabetics were more likely to present with dyspnea but less likely to present with ischemic chest pain. With regards to atypical chest pain, no significant differences were noted between the groups. The ST depression was more common in diabetic patients when compared to non-diabetics; however, ST elevation was less common in diabetics compared to non-diabetics. There were no differences in the patterns of left bundle branch block between the 2 groups. Diabetic patients were less likely to present with ST elevation myocardial infarction but more likely to present with unstable angina, when compared to non-diabetic patients.

Figure 1 shows in-hospital management of the cohort. Both, diabetic and non-diabetic patients received similar in-hospital management, but with 2 important differences. Both groups received aspirin, clopidogrel, thrombolytics, heparin, beta-blockers, lipid lowering agents, and in-hospital coronary angiography equally; however, diabetic patients were more likely to be treated with glycoprotein (GP) IIb/IIIa antagonists and angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers (ARBs).

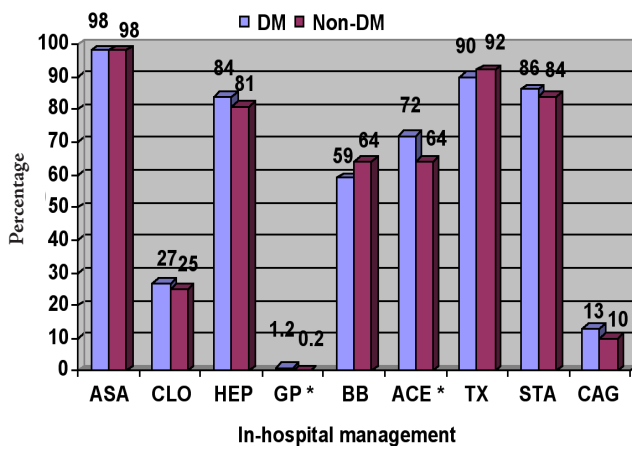

Figure 1 - In-hospital management of acute coronary syndrome patients with and without diabetes mellitus. DM - diabetes mellitus, ASA – aspirin, CLO – clopidogrel, HEP - heparin (includes low molecular weight heparin), GP - glycoprotein IIb/IIIa inhibitors, BB - beta-blockers, ACE - angiotensin-converting enzyme inhibitors (includes angiotensin II receptor blockers), TX – thrombolytics, STA – statins, CAG - coronary angiography. *significant *p*-value of <0.05.

Table 2 shows the complications encountered by the patients. Overall, the rates of individuals with in-hospital complications were significantly higher in the diabetic versus non-diabetic patients. Diabetic patients experienced more recurrent ischemia, heart failure, cardiogenic shock, and ventilator requirement while in the hospital. In-hospital mortality was higher in the diabetic group than that in the non-diabetic group, though the difference between the groups was not statistical significant. When adjusted for age and gender, diabetes status was an independent risk factor of in-hospital mortality in ACS patients (adjusted odds ratio, 1.68; 95% confidence interval, 1.02–2.77; *p*=0.042).

Discussion. In this study, 37% of patients with ACS in Oman were diabetic. This proportion is high compared with Western countries, but lower than the rest of the Gulf (40%),[11] and Saudi Arabia (53%).[12] In the multinational Gulf RACE study, 25% of ACS patients were diabetic.[3] According to European statistics, 20-35% of all ACS patients are diabetic.[13] It is known that the prevalence of diabetes is increasing especially in Middle Eastern countries and it will double by 2030.[9,14] Hence, this high prevalence rate of diabetes in Middle East ACS patients may not be surprising. The Framingham study demonstrated that atherosclerotic coronary artery disease is at least twice as common in men, and 4 fold more so in women with diabetes.[15] In our study, female patients with ACS were significantly more diabetic when compared to male patients with ACS. Diabetic patients had higher percentages of angina, aspirin use, higher BMI, hyperlipidemia, and hypertension, and they were more likely to have a prior diagnosis of peripheral vascular disease, dialysis, and prior history of stroke. This is

Table 2 - In-hospital outcome in acute coronary syndrome diabetic and non diabetic patients.

Characteristic	DM (n=588)	Non-DM (n=995)	*P*-value
Recurrent ischemia	68 (11.5)	84 (8.4)	0.043
Re-infarction	16 (2.7)	22 (2.2)	0.523
Congestive heart failure	171 (29)	231 (23)	0.009
Ventilation	43 (7.3)	41 (4.1)	0.006
Cardiogenic shock	44 (7.5)	46 (4.6)	0.018
Major bleed	5 (0.9)	12 (1.2)	0.505
Stroke	9 (1.5)	7 (0.7)	0.113
Mortality	33 (5.6)	38 (3.8)	0.096

DM - diabetes mellitus, percents are column percentages. All values n (%) unless specified.

similar to previous studies.[3,4,16] All these factors indicate that diabetic patients suffer from a diffuse endothelial dysfunction leading to multiple vascular complications. This study demonstrates that ACS patients with diabetes have different clinical characteristics. There is a general perception that patients with diabetes are less likely to experience angina than patients without diabetes. In this study, diabetic patients predominantly presented with ischemic chest pain. Furthermore, they were more likely to present with unstable angina and non-ST elevation myocardial infarction. This has also been noted in previous studies.[3,4,16]

Diabetes mellitus is a strong independent predictor of adverse outcomes for patients admitted across the entire spectrum of ACS.[2-5,16] In this study; diabetic patients experienced more recurrent ischemia, congestive heart failure, cardiogenic shock, and ventilator requirement while in the hospital. Many factors contribute to this adverse outcome in diabetic patients, such as severe diffuse multivessel coronary artery disease, autonomic dysfunction, and diabetic cardiomyopathy. Diabetic cardiomyopathy is a specific entity that influences the systolic and diastolic function, and may predispose these patients to develop more heart failure, cardiogenic shock, and pulmonary edema requiring ventilator management.[17] McGuire et al[18] noted that recurrent ischemia occurred more in diabetic patients. This is due to an exaggerated prothrombotic and inflammatory state in diabetic patients with ACS leading to increased risk of plaque rupture and thrombosis. This is attributed to multiple factors including abnormal platelet activation and thrombin-generation that are pronounced in diabetes, increased fibrinogen/von-Willebrand factor levels, decreased fibrinolysis, insulin resistance/hyperinsulinemia, autonomic, and endothelial dysfunction, as well as increased fatty acid turnover causing more oxygen consumption, all of which might predispose diabetic patients to recurrent ischemic events.

Several studies have demonstrated that ACS patients with diabetes had poor prognosis both in the acute phase and during long term follow up.[2-5,16] Our analysis demonstrates a statistically significant association between diabetes at time of presentation with ACS and in-hospital mortality after adjusting for age and gender. The Gulf RACE multinational registry also demonstrated diabetes for ACS patients to be a significant contributor to in-hospital and 6-month out-of-hospital mortality.[3] It has been noted that, in the setting of severe hyperglycemia there is decreased collateral circulation, increased infarct size, reduced ischemic preconditioning, microvascular dysfunction, increased pro-inflammatory factors like C-reactive protein, increased apoptosis, elevated catecholamine levels along with elevated blood pressures and QT prolongation.[19] Hyperglycemic patients with ST-elevation myocardial infarction have lower rates of spontaneous reperfusion.[17] In addition, autonomic neuropathy in diabetic patients results in disturbances of myocardial blood flow, myocardial function, and reduced heart rate variability, leading to arrhythmias and worsening heart failure.[17] Higher free fatty acid concentrations have been linked to increased incidence of malignant ventricular arrhythmias.

In this study, there were no differences involving thrombolytic therapy or coronary angiography in patients with diabetes, which is in contrast to previous studies.[3,16] However, in both groups the use of in-hospital coronary angiography and GP IIb/IIIa antagonists was very low. This could be one of the reasons for poorer outcomes in diabetic patients in our study. We found that despite advances in the medical treatment of ACS and diabetic patients receiving ACEI or ARBs as well as GP IIb/IIIa antagonists (though only a small percent) more compared to non-diabetic patients, the in-hospital mortality among patients with diabetes was still significantly higher. Our study highlights the need to apply guideline recommended therapy among ACS patients from Oman and calls for major research initiatives to identify new strategies to manage ACS among this high-risk population.

Roffi et al[20] noted that diabetic patients with ACS derive greater benefit from evidence-based therapy than non-diabetic individuals. Triple anti-platelet therapy - aspirin, clopidogrel, and GP IIb/IIIa receptor inhibitors along with unfractionated heparin or enoxaparin is of proven benefit in diabetic patients with ACS.[21] For low- or medium-risk individuals, a treatment based on aspirin, clopidogrel, and bivalirudin is suggested as a valuable alternative.[22] Prasugrel, a new and more potent inhibitor of the platelet P2Y(12) receptor, has proved to be more beneficial for diabetic patients with ACS.[23] Invasive coronary angiography followed by revascularization has to be undertaken in diabetic patients as per recommended guidelines. According to recent American Heart Association statement, insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among ACS patients.[19] Whether insulin-mediated normoglycemia will improve survival and reduce complications in patients with ACS remains to be established.[19]

The major limitation of our study is its retrospective analysis of a prospective registry and possible confounding by variables not controlled, as this was an observational study. However, despite age and gender adjustment, diabetes mellitus was still an independent risk factor for in-hospital mortality.

In conclusion, ACS patients with diabetes have

different clinical characteristics and poorer outcomes. Present treatment strategies are not sufficient to counter the adverse impact of diabetes. More effective and evidence-based therapeutic strategies should be identified and used in diabetic patients who develop ACS.

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