ARTICLE ORIGINAL

Prognostic impact of diabetes mellitus on patients managed by urgent percutaneous coronary intervention

Impact pronostic du diabète sucré chez les patients traités par angioplastie coronaire urgente

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Abstract

Introduction: Diabetes Mellitus (DM) is known to be associated with worse outcomes following percutaneous coronary intervention (PCI).
Aim: To assess prognostic impact of DM on patients managed by urgent PCI following ST-segment elevation myocardial infarction (STEMI).
Methods: In a retrospective study, STEMI patients admitted to our department from January 2016 to December 2019 and treated with urgent PCI (primary or rescue PCI) were included. They were divided in two groups: Diabetic and non-diabetic patients. They were followed-up for a period of 12 months. Major cardiac adverse event (MACE) was a composite outcome of the following events: myocardial infarction, target vessel revascularization, target lesion revascularization or cardiovascular death. MACEs were collected during follow-up.
Results: Our population consisted of 225 patients. DM was observed in 104 STEMI patients (46.2%). Diabetic patients had higher frequency of hypertension (p<0.001), low-density lipoprotein cholesterol levels > 1.4mmol/l (p<0.001) and chronic kidney disease (CKD) (p=0.009). In-hospital and 12-months mortality were significantly higher in the diabetic group (11.5% versus 4.1%; p=0.036) and (24.7% versus 8.7%; p=0.003). In-hospital and 12-months MACEs were also more frequent among diabetic patients (17.3% versus 6.7%; p=0.013) and (43.5% versus 17.5%; p<0.001). Main factors associated with in-hospital mortality among diabetic patients were age > 75 years, anemia, CKD, cardiogenic shock and procedural failure. Age > 75 years, hyperglycemia at admission (>10mmol/l), extensive anterior infarction and procedure failure were associated with in-hospital mortality in the non-diabetic group. Factors associated with 12-months mortality and MACEs among diabetic patients were age > 75 years, anemia, CKD and left ventricular systolic dysfunction.
Conclusions: Despite modern era of STEMI treatment, diabetic patients still have a poor prognosis. These results highlight the need for coronary risk factors treatment among these patients.

Key words: STEMI, Outcomes, Mortality, Major adverse cardiac event.

RÉSUMÉ

Introduction: Le diabète sucré (DS) est connu pour être associé à un plus mauvais pronostic après une angioplastie coronaire transluminale (ACT).
Objectif: Evaluer l'impact pronostic du DS sur les patients traités par ACT en urgence pour un syndrome coronarien aigu avec sus-décalage persistant du segment ST (STEMI).
Méthodes: Dans une étude rétrospective, les patients admis à notre service pour STEMI de janvier 2016 à décembre 2019 et traités par ACT urgente (ACT primaire ou de sauvetage) ont été inclus. Ils ont été divisés en deux groupes : patients diabétiques et patients non-diabétiques. Ils étaient suivis sur une période de 12 mois. Les évènements cardiaques majeurs (ECM) étaient un critère composite associant: infarctus du myocarde, revascularisation du vaisseau cible, revascularisation de la lésion cible ou décès d'origine cardiovasculaire. Les ECM ont été recueillis durant le suivi.
Résultats: Notre population a compris 225 patients. Le DS a été observé chez 104 patients (46,2%). Les patients diabétiques avaient une prévalence plus élevée d'hypertension (p<0,001), de taux de low-density lipoprotein cholestérol > 1.4mmol/l (p<0,001) et d'insuffisance rénale chronique (IRC) (p=0,009). Les mortalités intra-hospitalière et à 12 mois étaient plus élevées chez les diabétiques (11,5% versus 4,1%; p=0,036) et (24,7% versus 8,7%; p=0,003). La survenue d'ECM en intra-hospitalier et à 12 mois étaient également plus élevée chez les diabétiques (17,3% versus 6,7%; p=0,013) et (43,5% versus 17,5%; p<0,001). Les principaux facteurs de mortalité intra-hospitalière dans le groupe des diabétiques sont l'âge > 75ans, l'anémie, l'IRC, le choc cardiogénique et l'échec procédural. L'âge avancé, l'hyperglycémie à l'admission (> 10mmol/l), l'infarctus antérieur étendu et l'échec procédural étaient associés à plus de mortalité intra-hospitalière chez les non-diabétiques. Les facteurs prédictifs de mortalité et d'ECM à 12 mois chez les diabétiques étaient l'âge avancé, l'anémie, l'IRC et la dysfonction systolique du ventricule gauche.
Conclusion: Malgré les nouveaux traitements, les patients diabétiques gardent encore un mauvais pronostic. Ces résultats démontrent l'intérêt du contrôle des facteurs de risque parmi ces patients.

Mots clés: STEMI, Résultats, Mortalité, Evènement cardiaque majeur.

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INTRODUCTION

Coronary artery disease is a major public health problem. It is the leading cause of death in the world (1). It is also the leading cause of death in Tunisia in 2014 according to World Health Organisation (WHO). ST-segment elevation myocardial infarction (STEMI) requires a rapid diagnosis and immediate revascularization to prevent complications. Diabetes mellitus (DM) is a major cardiovascular risk factor. Compared to the general population, diabetic patients have a more complex coronary anatomy, have more co-morbidities, and are at higher risk of developing complications following percutaneous coronary intervention (PCI) such as stent thrombosis and intracoronary stent restenosis (2). Diabetic patients who develop STEMI, compared to non-diabetic patients present to the emergency department with longer ischemia time, have more hemodynamic instability and frequently get later revascularization (3). This may explain the worse prognosis associated with DM.
National registries of STEMI among diabetic patients are lacking. Furthermore, few studies about this issue have been published in Tunisia.
The aim of our study was to assess prognostic impact of DM on patients managed by urgent PCI following STEMI.

METHODS

It was an observational, monocentric, retrospective study. From January 2016 to December 2019, patients presenting via emergency medical system with STEMI and treated in the cardiology department of Farhat Hached university hospital center with urgent PCI (primary PCI or rescue PCI) were included. STEMI patients with successful reperfusion after fibrinolytic therapy and STEMI patients who presented after resolution of chest pain (typically more than 24 hours from chest pain onset) were not included. Patients with medical files missing data were excluded. All patients received pre-treatment with aspirin and P2Y12 inhibitors. Anticoagulation with unfractionated heparin was administred following the local protocol (70 IU/kg i.v.). Ethical approval was obtained from the hospital local committee. All patients provided written informed consent before inclusion. Patients were divided in two groups: Diabetic group and non-diabetic group.

Baseline characteristics were collected from medical files. They included: age, sex, DM, hypertension, active smoking (or stopped for less than 3 years) and past medical history including previous myocardial infarction, previous stroke or transient ischemic attack, as well as a known chronic kidney disease (CKD) defined as a glomerular filtration rate < 60ml/min according to modification of diet in renal disease (MDRD) equation. Biological variables were analyzed at admission. They included hemoglobin, serum creatinine, blood glucose and low-density lipoprotein (LDL) cholesterol. Anemia was defined as a hemoglobin level < 12g/dl in women and <13g/dl in men. The considered cut-off for LDL-cholesterol was 1.4mmol/l. hyperglycemia at admission was defined as blood glucose level > 10mmol/l. Extensive anterior infarction was defined as ST-segment elevation in all precordial leads (V1 through V6), DI and aVL. Patients were hemodynamically evaluated before admission to catheterization laboratory. Cardiogenic shock was defined as “Systolic blood pressure < 90 mmHg and signs of hypoperfusion (cool clummy skin, oliguria or altered sensorium), nonresponsive to fluid resuscitation or pressors” (4).

For primary PCI, symptoms-to-first medical contact and door-to-balloon delays were analyzed. For rescue PCI, symptoms-to-fibrinolytic therapy and fibrinolytic therapy failure-to-balloon delays were analyzed.

Procedural aspects were specified. They included type of PCI (primary or rescue PCI), access route, infarct related artery, type of stents used (drug-eluting stents (DES) or bare-metal stents (BMS)), pre-procedural and post-procedural thrombolysis in myocardial infarction (TIMI) flow, thromboaspiration use and Gp IIb-IIIa inhibitors use. All DES used were second generation (Sirolimus-eluting stents or Everolimus-eluting stents). Procedure failure was defined as the absence of post-procedural TIMI flow 3.

Echocardiography was performed to all patients 24 hours after PCI. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction less than 40%.

Major adverse cardiac event (MACE) was a composite outcome defined as the occurrence of myocardial infarction, target vessel revascularization, target lesion revascularization or cardiovascular death. MACEs and mortality were recorded during the hospital stay and for the next 12 months.

For statistical analysis, categorical data were presented as counts and proportions (%). Continuous data were presented as median or as mean ± standard deviation, as appropriate. Differences between groups were evaluated using the Student t tests for continuous data. Chi-squared or Fisher exact tests (if the expected cell value was under 5) were used for categorical variables. Factors associated with mortality and MACEs were identified by univariate and multivariate logistic regression analysis. Odds ratio (OR) and confidence intervals at 95% (95% CI) were calculated. All probability values were two sided and considered statistically significant if $p<0.05$.

RESULTS

Baseline characteristics

Our population included 225 STEMI patients. Diabetic patients represented 46.2% (104). Baseline characteristics are represented in table 1. Hypertension, CKD, anemia and high LDL-cholesterol levels were more frequent in the diabetic group. However, smoking and hyperglycemia at admission were more frequent in the non-diabetic group.

Table 1. Baseline characteristics in the population study and according to diabetes mellitus

Variables	Population study (n=225)	Diabetic group (n=104)	Non-Diabetic group (n=121)	P value
Age, mean ± SD (years)	61.1 ± 11.8	62.4 ± 11	59.9 ± 12.3	NS
Age > 75 years	39 (17.3 %)	19 (18.3 %)	20 (16.5 %)	NS
Sex, male (%)	167 (74.2 %)	73 (70.2 %)	94 (77.7 %)	NS
Hypertension (%)	78 (34.8 %)	50 (48.1 %)	28 (23.1 %)	<0.001
Active smoking (or stopped for less than three years) (%)	149 (66.2 %)	56 (53.8 %)	93 (76.9 %)	<0.001
High LDL-cholesterol (> 1.4 mmol/l) (%)	88 (39.1 %)	56 (53.8 %)	32 (26.4 %)	<0.001
Anemia*	55 (24.4 %)	36 (34.6 %)	19 (15.7 %)	0.004
Hyperglycemia (> 10 mmol/l) (%)	77 (34.2 %)	73 (70.2 %)	4 (3.3 %)	<0.001
Past medical history				
MI (%)	22 (9.8 %)	9 (8.7 %)	13 (10.7 %)	NS
Stroke or TIA (%)	11 (4.9 %)	6 (5.8 %)	5 (4.1 %)	NS
CKD (%)	36 (16.8 %)	28 (26.9 %)	8 (6.6 %)	0.009
Cardiogenic shock (%)	21 (9.1 %)	12 (11.5 %)	9 (7.4 %)	NS
Extensive anterior infarction (%)	19 (8.4 %)	8 (7.7 %)	11 (9.1 %)	NS
Left ventricular systolic dysfunction**	60 (26.7 %)	25 (24.1 %)	35 (29 %)	NS

CKD: chronic kidney disease defined as a glomerular filtration rate < 60ml/min according to modification of diet in renal disease (MDRD) equation.; LDL-cholesterol: low-density lipoprotein cholesterol; MI: Myocardial infarction; NS: not significant (p value >0.05); SD: standard deviation; TIA: Transient Ischemic attack.
*Anemia is defined as a hemoglobin level < 12g/dl in women and <13g/dl in men.
** Left ventricular systolic dysfunction is defined as left ventricular ejection fraction less than 40%.

Reperfusion delays

For primary PCI, symptoms-to-first medical contact mean delay was 8.66 ± 6.75 hours and door-to-balloon mean delay was 1.5 ± 1.14 hours. These delays were similar in both the diabetic group and the non-diabetic group. (9.2 ± 6.95 hours vs. 8.2 ± 6.60 hours; p=0.405 and 1.58 ± 1.15 hours vs. 1.44 ± 1.14 hours; p=0.51 respectively).

For rescue PCI, symptoms-to-fibrinolytic therapy mean delay was 5.07 ± 3.75 hours and fibrinolytic therapy failure-to-balloon mean delay was 5.79 ± 4.54 hours. Similarly, there was no difference in these mean delays between diabetic and non-diabetic patients (5.27 ± 3.31 hours vs. 4.90 ± 4.12 hours; p=0.675 and 5.91 ± 3.82 hours vs. 5.70 ± 5.1 hours; p=0.846 respectively).

Procedural aspects

Procedural aspects in the population study and according to DM are summarized in table 2. There was no difference between diabetic and non-diabetic patients except for DES use which was more frequently implanted in the diabetic group (33.7 % vs. 14.9 %; p=0.002).

Table 2. Procedural aspects in the population study and according to diabetes mellitus

Variables	Population study (n=225)	Diabetic group (n=104)	Non-Diabetic group (n=121)	P value
Type of PCI				
Primary PCI (%)	149 (66.2 %)	68 (65.4 %)	81 (66.9 %)	NS
Rescue PCI (%)	76 (33.8 %)	36 (34.6 %)	40 (33.1 %)	
Access route				
Trans-radial access route (%)	148 (65.8 %)	73 (70.2 %)	75 (62 %)	NS
Trans-femoral access route (%)	77 (34.2 %)	31 (29.8 %)	46 (38 %)	
Pre-procedural TIMI flow (%)				
0-1	118 (52.4 %)	51 (49 %)	67 (55.4 %)	NS
2	58 (25.8 %)	27 (26 %)	31 (25.6 %)	NS
3	49 (21.8 %)	26 (25 %)	23 (19 %)	NS
Procedural failure (%)	37 (16.4 %)	20 (19.2 %)	17 (14 %)	NS
DES* (%)	53 (23.6 %)	35 (33.7 %)	18 (14.9 %)	0.002
Thrombo-aspiration use (%)	34 (15.1 %)	12 (11.5 %)	22 (18.3 %)	NS
Glycoprotein IIb-IIIa inhibitors use (%)	45 (25 %)	18 (17.3 %)	27 (22.3 %)	NS
Infarct-related artery (%)				
LM	4 (1.8 %)	2 (1.9 %)	2 (1.7 %)	NS
LAD	124 (55.1 %)	55 (52.9 %)	69 (57 %)	NS
LCX	29 (12.9 %)	13 (12.5 %)	16 (13.2 %)	NS
RCA	68 (30.2 %)	34 (32.7 %)	34 (28.1 %)	NS

DES: Drug-eluting stent; LAD: Left anterior descending artery; LCX: Left circumflex artery; LM: Left Main; NS: not significant (p value >0.05); PCI: percutaneous coronary intervention; RCA: right coronary artery;
* All DES used were second generation (Sirolimus-eluting stents or Everolimus-eluting stents)

In-hospital and 12-months outcomes

Table 3 summarizes outcomes of the population study and according to DM. In-hospital and 12-months mortality and MACEs were higher in the diabetic group compared to the non-diabetic group.

Table 3. In-hospital and 12-months outcomes according to diabetes mellitus

Outcomes	Population study (n=225)	Diabetic group (n=104)	Non-diabetic group (n=121)	P value
In-hospital outcomes				
Mortality (%)	17 (7.6 %)	12 (11.5 %)	5 (4.1 %)	0.036
MACEs (%)	26 (11.6 %)	18 (17.3 %)	8 (6.6 %)	0.013
12-months outcomes				
Mortality (%)	35 (15.6 %)	25 (24.1 %)	10 (8.3 %)	0.003
MACEs (%)	66 (29.3 %)	45 (43.5 %)	21 (17.4 %)	<0.001

MACEs: major adverse cardiac events

Main predictors of worse outcomes according to diabetes mellitus

- Factors associated with in-hospital mortality

Factors associated with in-hospital mortality and identified by univariate analysis are summarized in table 4. Age > 75 years and procedural failure were associated with in-hospital mortality in both the diabetic and the non-diabetic group. Anemia, CKD and cardiogenic shock were predictors of mortality among diabetic patients only. Extensive anterior infarction and hyperglycemia at admission were associated with in-hospital mortality in the non-diabetic group. Independent factors associated with in-hospital mortality and identified by multivariate logistic regression in the diabetic group were CKD [OR 6.22; 95% CI 1.24 – 31.07; p=0.026], cardiogenic shock [OR 6.82; 95% CI 1.16 – 40.13; p=0.034] and procedure failure [OR 6.23; 95% CI 1.67 – 40.5; p=0.0]. Only extensive anterior infarct was independently associated with in-hospital mortality in the non-diabetic group [OR 6.2; 95% CI 6.12 – 34.27; p<0.001] (Table 5).

- Factors associated with 12-months mortality and MACEs

Factors associated with 12-months mortality among patients with DM, as demonstrated in table 6, were age > 75 years, anemia, CKD and left ventricular systolic dysfunction. These same factors were also associated with 12-months MACEs and none of them was considered statistically significant to predict worse outcomes in the non-diabetic group.

Independent factors associated with 12-months mortality among diabetic patients identified by multivariate logistic regression were CKD [OR 9.32; 95% CI 2.13 – 40.93; p=0.003] and left ventricular systolic dysfunction [OR 4.88; 95% CI 1.1 – 21.65; p<0.001]. Anemia and left ventricular systolic dysfunction were independent predictors of 12-months MACEs in the diabetic group: [OR 9.11; 95% CI 2 – 41.46; p=0.004] and [OR 4.06; 95% CI 1 – 16.82; p<0.048] respectively.

Table 4. Factors associated with in-hospital mortality according to diabetes mellitus (univariate analysis).

	Diabetic group		*Non-diabetic group*	
	Mortality (%)	**P value**	**Mortality (%)**	**P value**
Age > 75 years	31.5 vs. 7	0.008	15 vs. 2	0.031
Anemia*	22.8 vs. 4.7	0.006	10 vs. 3.3	0.22
CKD	33.3 vs. 3.9	<0.001	8.3 vs. 2.9	0.363
Cardiogenic shock	50 vs. 6.5	<0.001	0 vs. 4.5	1
Extensive anterior infarction	12.5 vs. 11.4	1	36.3 vs 0.9	<0.001
Procedure failure	35 vs. 5.9	0.002	17.6 vs 1.9	0.02
Hyperglycemia at admission (>10mmol/l)	13.7 vs. 10	1	75 vs 2	<0.001

CKD: chronic kidney disease defined as a glomerular filtration rate < 60ml/min according to modification of diet in renal disease (MDRD) equation.
*Anemia is defined as a hemoglobin level < 12g/dl in women and <13g dl in men.

Table 5. Independent factors associated with worse outcomes (multivariate logistic regression analysis)

	Odds ratio	**Confidence interval at 95 %**	**P value**
Independent factors associated with in-hospital mortality in the diabetic group			
CKD	6.22	1.24 – 31.07	0.026
Cardiogenic shock	6.82	1.16 – 40.13	0.034
Procedure failure	6.23	1.67 – 40.5	0.01
Independent factors associated with in-hospital mortality in the non-diabetic group			
Extensive anterior infract	6.2	6.12 – 34.27	<0.001
Independent factors associated with 12-months mortality in the diabetic group			
CKD	9.32	2.13 – 40.93	0.003
Left ventricular systolic dysfunction*	4.88	1.1 – 21.65	<0.001
Independent factors associated with 12-months MACEs in the diabetic group			
Anemia**	9.11	2 – 41.46	0.004
Left ventricular systolic dysfunction*	4.06	1 – 16.82	0.048

CKD: chronic kidney disease defined as a glomerular filtration rate < 60ml/min according to modification of diet in renal disease (MDRD) equation; MACEs: major adverse cardiac events.
* Left ventricular systolic dysfunction is defined as left ventricular ejection fraction less than 40%.
**Anemia is defined as a hemoglobin level < 12g/dl in women and <13g/dl in men.

Table 6. Main factors associated with 12-months mortality and major adverse cardiac events according to diabetes mellitus (univariate analysis).

	Diabetic group		Non-diabetic group	
	Mortality (%)	**P value**	**Mortality (%)**	**P value**
Age > 75 years	52.9 vs. 17.6	0.007	17.6 vs. 6.9	0.166
Anemia*	46.8 vs. 10	<0.001	11.1 vs. 9.2	0.681
CKD	61.9 vs. 11.3	<0.001	10 vs. 7.9	0.592
Left ventricular systolic dysfunction**	47 vs. 8.9	<0.001	20 vs. 5.3	0.052
	MACEs	**P value**	**MACEs**	**P value**
Age > 75 years	70 vs. 36.7	0.012	23.5 vs. 16.3	0.491
Anemia*	68.7 vs. 28	<0.001	16.7 vs. 17.1	0.483
CKD	57.1 vs. 33.2	<0.001	20 vs. 17	0.683
Left ventricular systolic dysfunction**	70 vs. 26.8	<0.001	32 vs. 15.8	0.096

CKD: chronic kidney disease defined as a glomerular filtration rate < 60ml/min according to modification of diet in renal disease (MDRD) equation; MACEs: major adverse cardiac events.
*Anemia is defined as a hemoglobin level < 12g/dl in women and <13g/dl in men.
** Left ventricular systolic dysfunction is defined as left ventricular ejection fraction less than 40%.

DISCUSSION

The main finding of our study was that DM is associated with higher rates of mortality and MACEs compared to non-diabetic patients. Many studies have reported similar findings (5,6).
It has been demonstrated that hyperglycemia at admission (stress hyperglycemia) is associated with larger infarct size and higher mortality in STEMI patients (7). Stress hyperglycemia is most probably induced by the acute release of catecholamine, cytokines and cortisol in the acute stage of MI, but the mechanisms have not been fully elucidated (8). Marfella et al. reported increased intercellular adhesion molecule-1 levels (9) which could augment plugging of leucocytes in the capillaries (10).
DM is also associated with higher rates of intracoronary stent restenosis (ISR) (11). Several possible factors can accelerate many of the pathophysiological processes that lead to the higher restenosis rate in the diabetic patients, and mainly because of the alternation of endothelial cell function. Wei-Wen Chan described the peroxisome proliferator activated receptors that are effective in reducing plaque inflammation by inhibiting expression of adhesion molecules and formation of cytokines (12). The elevation and reduction of the aforementioned factors in patients with DM compared with patients without DM cause the following processes: pro-inflammatory state, pro-thrombotic state, accelerated and unstable plaque formation and hemodynamic changes caused by narrowing of vessel diameter, thereby leading to restenosis and plaque formation.
Noman et al. have also reported higher rates of intra-stent complications among diabetic patients (7). Actually, resistance to clopidogrel has been described among diabetic patients. Several factors may explain why diabetics more commonly have an impaired response to clopidogrel compared to non-diabetics. These include insulin resistance, poor glycemic control, and increased inflammatory status (7). Platelets from diabetic patients are poorly responsive to insulin, show an increased response to adenosine diphosphate, and have heightened activity on contact with collagen (13). Moreover, diabetic patients with poor glycemic control have increased platelet reactivity despite dual antiplatelet therapy (14). Ang et al. recently showed that increased plasma fibrinogen is significantly associated with a lower response to clopidogrel in patients with DM, possibly due to a direct interaction of fibrinogen with the glycoprotein IIb/IIIa receptor (15). Furthermore, in diabetic patients increased production of platelet agonists, such as epinephrine and thrombin receptor agonist peptide, may explain the higher levels of platelet activation through different signaling pathways besides those depending on the P2Y12 receptor (16). Thus, in patients with DM a global hyper-reactive platelet status is present, which may explain low responsiveness even after higher maintenance doses of antiplatelet drugs (17). All these factors may explain higher mortality and MACEs in the diabetic group as shown in our study.

Limitations of our study

It was a retrospective study. Some data were lacking. Moreover, the number of patients was limited compared to large published studies, thus, CI were quite large. Further prospective studies should be conducted to offer more information and allow better analysis of DM impact on patients managed by urgent PCI.

CONCLUSIONS

Despite modern era of STEMI treatment, diabetic patients still have a poor prognosis compared to non-diabetic patients. These results highlight the urgent need for coronary risk factors control and particular attention should be given to diabetic patients who survived myocardial infarction.

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