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Incidence of Acute Myocardial Infarction in Patients with Diabetes and Its Association with Mortality and Cardiopulmonary Complications in Puerto Rico

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Abstract Diabetes mellitus (DM) patients are at an increased risk of acute myocardial infarction (AMI). Adequate DM control may reduce in-hospital mortality and cardio-pulmonary complications after an AMI. The objective of this study was to determine whether uncontrolled DM in patients with an incidental AMI was associated with an increased risk of in-hospital mortality and selected cardio-pulmonary complications. A secondary data analysis of the Puerto Rican Cardiovascular Surveillance System during 2007, 2009, and 2011 was conducted. The study included men and women living in Puerto Rico who were hospitalized due to an incidental AMI and had information on HbA_{1c} measurement (n=220). Patients were divided according to their HbA_{1c} levels into two groups (i) <7% (controlled); and (ii) ≥7% (uncontrolled). Mortality and complications were defined according to ICD-9 codes. Univariate and multivariate logistic regression models were used to test for associations between HbA_{1c} and mortality and cardio-pulmonary outcomes. The model was adjusted for gender, obesity (BMI >30kg/$m^{2)}$, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, smoking, insurance and age. The results revealed no statistically significant association between the controlled and the uncontrolled DM patients and mortality, respectively cardiopulmonary complications (unadjusted OR 2.1; 95% CI: 0.7-6.4; adjusted OR 2.4; 95% CI: 0.5-10.5). The uncontrolled DM group was statistically significantly younger than those with controlled DM (mean age 65.2 vs. 71.1 years; p-value 0.002). There was no statistically significant difference in the prevalence of uncontrolled DM between patients with complications (80%) and those without complication (66%; p=value 0.203). AMI patients with uncontrolled DM did not have an increased risk of mortality and cardiopulmonary complications compared to patients with controlled DM. This needs further evaluation in a larger study population and DM patients with an AMI should have HbA1c measured to estimate their risk of complications.

Keywords: *Diabetes, acute myocardial infarction, mortality, cardiopulmonary complications, glycosylated hemoglobin (HbA1c)*

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1. Introduction

Diabetes mellitus (DM) is a growing epidemic that has affected people from all regions and has become a rising global burden [1]. It has affected the health condition of millions as well as developed into a financial liability internationally. In 2015 there was an estimated 415 million people with DM and over 5 millions deaths due to the disease [1,2]. This chronic condition seems to affect all systems of the body, but the most common cause of death and disability was due to cardiovascular disease [1]. People with DM have a higher prevalence of coronary artery disease (CAD) leading to an increased risk of myocardial infarction (MI), mortality, and other cardiopulmonary complications. The National Cholesterol Education Program report from the United States and European guidelines consider DM to be a coronary heart disease (CHD) equivalent, thereby elevating it to the highest risk category [1]. This classification was based on coronary mortality for patients with DM without a prior MI and patients without DM who had a prior MI [2]. According to the American Diabetes Association (ADA) [4], the assessment of HbA_{1c} levels in diabetes patients are categorized as good control (<7%), suboptimal control

(HbA_{1c} 7% to 9%), or poor control (HbA_{1c} >9%)[4]. Poor long-term glycemic control is an important risk factor for adverse outcomes in patients with DM [4]. Epidemiologic studies suggest that an increase in HbA_{1c} of 1% is associated with a 20% increased risk in subsequent mortality for patients with coronary disease and concurrent DM [4]. Information regarding associations between DM control and *3*0 days in-hospital survival are contradictory [5,8,9]. Previous studies had controversial results with several limitations that included selection bias [6], small sample size causing low power to detect differences, and focus on special subgroups of the population [12].

The aim of our study was to investigate whether diabetes control was associated with mortality and cardiopulmonary complications such as atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiac arrest, pulmonary infarction, pulmonary edema, respiratory failure, and stroke in DM patient with an incident AMI in Puerto Rico**.**

2. Materials and Methods

2.1. Study Design

We conducted a cross-sectional study of the Puerto Rican Cardiovascular Surveillance database during 2007, 2009 and 2011 [10].

2.2. Study Population

All previous health records were reviewed before including a patient. The definition used in this study as inclusion criteria for T2DM was previous history of DM found in the medical records according to the ADA. After a patient was found to have the diagnosis of T2DM, the record was reviewed to see if HbA_{1c} levels were recorded to be included in the study**.** Only those with HbA_{1c} measurements taken within the first 24 hours were included. The inclusion criteria for an AMI was that each case was validated using the widely accepted diagnostic definition developed by the World Health Organization (WHO) [4] This definition requires that at least two out of three criteria be present for the confirmation of AMI. This uses information from the patient's clinical history, serum enzyme elevations, and serial ECG findings. This secondary data analysis was conducted in patients presenting with an incidental (first time) AMI who had HbA_{1c} measures taken within the first 24 hours of hospital admission and reported in the medical chart. We included all patients with ICD-9 codes: 410-414; specifically: New MI, 411: Other acute/sub-acute forms ischemic heart disease, 412: Old MI, 413 Angina pectoris, and 414: Other forms of chronic ischemic heart disease, and excluded 412: patients with previous MI. The records of any previous hospitalizations for cardiovascular events were reviewed when available and if past records indicated similar presentation they were excluded from the study. We excluded patients who did not meet the diagnosis criteria for DM (n=1,138) as stated above, missing key variables of the study, had ECG changes consistent with previous MI, documented history of MI, patients who developed AMI from any procedural events during their hospital stay, and any cardiopulmonary complication the arises after 24 hours of initial hospital arrival. The cardiopulomanary complications that were included in our study was atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiac arrest, pulmonary infarction, pulmonary edema, respiratory failure, and stroke. All of these complications were documented in the patient's medical chart and had to be within 24 hours of admission The study population consisted of Puerto Ricans (a mostly Hispanic population) men and women with T2DM living on the Island who were hospitalized for an incidental AMI. In the database, there were 2,204 patients with an AMI during 2007, 2009, and 2011. A total of 1,470 patients were excluded for not having an incidental AMI or not being diagnosed with T2DM. Out of the remaining 734 patients, 532 were excluded, as they did not have information on HbA_{1c} measurement. Thus, 202 patients comprised our study population [10].

The study population was divided into two groups according to their HbA1C level: controlled DM ($HbA_{1c} \leq 7$) and uncontrolled DM (HbA_{1c} >7). The covariables that were analyzed in this study were age, gender, hypertension, obesity (defined as BMI>30kg/m^2), hyperlipidemia, chronic obstructive pulmonary disease (COPD), current cigarette smokers, and insurance status. These variables were selected because they were related to both HbA_{1c} levels as well as to AMI complications.

All data were obtained from medical documentation of each individual patient that was entered into the database system. Participants have been appropriately de-identified to maintain minimal risk exposure of sensitive information, which was our main concern when obtaining the data for our study.

2.3. Statistical Analysis

STATA version 14.0 was used for the statistical analysis. The medical records of patients discharged with a diagnosis consistent with AMI were reviewed utilizing a standardized electronic data abstraction form, which has been adapted to use in Puerto Rico from the Worcester Heart Failure Study. Data were captured electronically utilizing the REDCapTM web application exclusively designed for research studies that allows secure online management of surveys and databases. For the purpose of present analysis, patients were divided into controlled ($HbA_{1c} \leq 7\%$) and uncontrolled DM (, HbA_{1c} >7%) based on admission HbA_{1c}. Categorical variables are presented as percentage and number of patients and the continuous variable are presented as mean ± standard deviation. Baseline characteristics of the two groups were compared using the χ^2 test, t student test, and the Fisher exact test as appropriate. Logistic regression models (univariate and multivariate analysis) were used to test the association between the independent variable and the outcome variable, which is in-hospital mortality and cardiopulmonary complications. The Hosmer-Lemeshow test was used to test for the goodness-of-fit of the logistic regression models. The multivariate logistic regression model was adjusted for sex, age, body mass index (BMI), hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), current smokers, insurance status, and age. A p-value <0.05 was considered as statistically significant.

3. Results

Table 1 presents the characteristics of the study participants according to DM control (HbA_{1C}<7% versus HbA_{1C}≥7%). The only characteristic that was statistically significantly different was that the patients in the uncontrolled DM group were younger than those in the group with controlled DM (mean age 65.2 vs. 71.1 years; p-value 0.002). No statistically significant differences were found in the distribution of gender, obesity (BMI>30kg/m^2), hyperlipidemia, hypertension, COPD, current smokers, or insurance between the two groups.

The association between HbA_{1c}, mortality and cardio-pulmonary complications among DM patients are presented in Table 2. In the univariate analysis uncontrolled DM patients were twice as likely to die or to have complications than those that had DM controlled (OR 2.1; 95% CI: 0.7-6.4). After adjustment for gender, BMI>30 kg/m^2, hyperlipidemia, hypertension, COPD, current smokers, insurance status, and age the OR only marginally changed and remained statistically non-significant (OR 2.4; 95% CI: 0.5-10.3). The OR for an association between obesity and mortality was not statistically significant after multivariate adjustment (OR 0.8; 95% CI 0.2-2.8).

Table 1. Characteristics of diabetes mellitus (DM) patients with first time acute myocardial infarction according to DM control in Puerto Rico during 2007, 2009, and 2011

Characteristics	Controlled (HbA1C<7%) % (n)	Uncontrolled (HbA1C≥7%) % (n)	p-value
Sex		**% (n**	0.112
Male	47.0 (31)	58.8 (80)	
Female	53.0 (35)	41.2 (56)	
BMI[1] >30 kg/m[2]			0.109
No	37.0 (17)	24.3 (27)	
Yes	63.0 (29)	75.7 (84)	
Hyperlipidemia			0.413
No	63.1 (41)	68.9 (93)	
Yes	37.0 (24)	31.1 (42)	
Hypertension			0.526
No	18.2 (12)	14.7 (20)	
Yes	81.8 (54)	85.3 (116)	
COPD[2]			0.315
No	93.9 (62)	89.6 (121)	
Yes	6.1 (4)	10.4 (14)	
Current Smoker			0.564
No	86.2 (56)	83.0 (112)	
Yes	13.9 (9)	17.0 (23)	
Insurance			0.128
No	30.3 (20)	20.6 (28)	
Yes	70.0 (46)	79.4 (108)	
Age (years)- mean (SD[3])	71.1 (10.7)	65.2 (12.0)	0.002

[1]Body Mass Index; [2]Chronic Obstructive Pulmonary Disease; [3]Standard Deviation.

Table 2. Unadjusted and adjusted odds ratios for the association between HbA1c, mortality and complications among diabetes mellitus patients with first time acute myocardial infarction in Puerto Rico during 2007, 2009, and 2011

Characteristics	Unadjusted model (n=202) OR (95% CI)	Adjusted model (n=202) OR (95% CI)
HbA1c		
Control	Reference	Reference
Uncontrolled	2.1 (0.7-6.4)	2.4 (0.5-10.3)
Sex		
Male	Reference	Reference
Female	1.2 (0.5-3.1)	1.7 (0.5-5.6)
BMI[1]> 30 kg/m[2]		
No	Reference	Reference
Yes	0.8 (0.3-2.6)	0.8 (0.2-2.8)
Hyperlipidemia		
No	Reference	Reference
Yes	1.5 (0.6-4.0)	2.0 (0.6-6.8)
Hypertension		
No	Reference	Reference
Yes	1.1 (0.3-4.0)	0.7 (0.1-3.6)
COPD[2]		
No	Reference	Reference
Yes	0.5 (0.07-4.3)	0.3 (0.03-3.0)
Current Smoker		
No	Reference	Reference
Yes	1.4 (0.4-4.4)	2.6 (0.6-12.3)
Insurance		
Yes	Reference	Reference
No	0.8 (0.2-2.5)	0.7 (0.2-3.1)

Out of 734 DM patients with an AMI, only 202 had their HbA_{1c} levels measured (Table 3). DM patients without HbA1C measurement seemed to have a higher prevalence of mortality and complications (12.8%) compared to measured patients (9.9%). However, these results were not statistically significant (p=0.283). There was a higher prevalence of COPD in the group where HbA_{1c} was measured (9.0%) compared to those with no HbA_{1c} measured (4.7%; p-value=0.031). Furthermore, the prevalence of obesity (BMI>30 kg/m^2) was higher in the group who had HbA_{1c} measured (71.9%) compared to those who were not measured (62.8%; p-value=0.037). There was a higher distribution of patients with insurance in the group where HbA_{1c} was measured (76.2%) compared to those who did not have measurement (66.4%; p-value=0.010). There was no statistical significant difference in the rest of the characteristics studied.

Table 3. Characteristics of all previously diabetes mellitus patients with first time acute myocardial infarction according to whether HbA1C was measured or not in Puerto Rico during 2007, 2009, and 2011

Characteristics	HbA1c measured (N=202 % (n)	No HbA1c measured (N=532) % (n)	p-value
Mortality and complications			0.283
No	90.1 (182)	87.2 (464)	
Yes	9.9 (20)	12.8 (68)	
Sex			0.670
Male	54.9 (111)	53.2 (283)	
Female	45.1 (91)	46.8 (249)	
BMI[1] > 30 kg/m[2]			0.037
No	28.0 (44)	37.3 (165)	
Yes	71.9 (113)	62.8 (278)	
Hyperlipidemia			0.951
No	67.0 (134)	67.2 (353)	
Yes	33.0 (66)	32.8 (172)	
Hypertension			0.642
No	15.8 (32)	14.5 (77)	
Yes	84.8 (170)	85.5 (455)	
COPD[2]			0.031
No	91.0 (183)	95.3 (503)	
Yes	9.0 (18)	4.7 (25)	
Current Smoker			0.113
No	84.0 (168)	88.4 (465)	
Yes	16.0 (32)	11.6 (61)	
Insurance			0.010
No	23.8 (48)	33.7 (179)	
Yes	76.2 (154)	66.4 (353)	
Age-mean (SD[3])	67.0 (11.9)	67.9 (12.3)	0.430

[1]Body Mass Index; [2]Chronic Obstructive Pulmonary Disease; [3]Standard Deviation.

4. Discussion

Even though our study found that AMI patients with uncontrolled DM had a two-fold increased risk of mortality and cardiopulmonary complications compared to controlled DM, this risk increase was not statistically significant.

A possible explanation may be a power issue and future studies may adjust for this with a larger study population. This may reveal whether poor DM control is associated with in-hospital mortality and cardio-pulmonary complications. The assessment of chronic glycemic control is highly variable among patients with AMIs and DM. Because much of this variability occurs at the hospital level, the evaluation of DM control could represent an additional quality indicator and an opportunity to advance patient-centered AMI care [4]. Every year over 735,000 Americans citizens have an AMI and people with known DM have an increased risk [6,7]. In addition, it might be desirable to achieve HbA_{1c} as close to the normal glycemic range as possible [8].

Poor DM control has shown to increase the risk of mortality through several mechanisms [11]. When glucose levels are chronically elevated they damage blood vessels and make them more susceptible to atherosclerosis build up. This causes people to develop atherosclerosis at an early age, leading to hypertension and coronary artery disease [4]. DM patients are also more prone to develop dyslipidemia. Their LDL particles are smaller then non-diabetics making it easier to penetrate vessels. This makes the particles more susceptible to oxidation and damage [4]. Higher HbA_{1c} was associated with poor glycol-metabolic control, older patients, obesity, hypertension, Killip's class>1, tachycardia, initial bundle branch block, atrial fibrillation, and higher mortality during follow-up [5]. These patients with disturbed glucose metabolism had worse early outcomes, characterized by progressive increased rates of in-hospital mortality according to HbA_{1c}. In hospital mortality was 14% higher in patients with HbA1c >6.4% [7]. Diabetes patients with low or high HbA_{1c} are at higher risk of all cause mortality compared wit patients with relatively moderate Hba_{1c} levels [8]. This compared to our study by looking for similar outcomes in terms of mortality and cardiopulmonary complications. Our study also tried to looks for an increased risk of mortality and cardiopulmonary complications based on Hb_{a1c} levels. But our odds ratio was not statistically

significant and we had a wide confidence interval showing a lack of precision in our study.

Previous studies have shown that elevated glucose levels increase the risk of mortality after an AMI in both diabetic and non-diabetic patients [17]. Both DM and non-DM patients had significantly higher plasma glucose levels, while HbA1c-adjusted levels were not associated with post-AMI prognosis [19]. Our study did not analyze admission glucose but rather HbA_{1c} levels within 24 hours of admission. We did not find any significant evidence to support the claim that DM patients with AMI had increased mortality and complications. We also did not evaluate medical records past the initial 24 hours of hospital stay to evaluate long-term prognosis for patients with controlled and uncontrolled HbA_{1c} levels. A secondary data analysis of The National Cardiovascular Data Registry (NCDR) observed no association between HbA_{1C} and mortality in patients with diabetes presenting with AMI [18]. In a multivariable regression, they observed no association between low or high HbA_{1c} [18]. Similar to their study we did not find any statistically significant association between HbA_{1c} and mortality and complications. As their study, our study had similar limitations DM patients with AMI did not have information on HbA_{1c} measurement (59%). In another study Hba_{1c} and blood glucose was measured within 3 hours of admission of an AMI to evaluate for myocardial perfusion abnormalities [15]. Patients with the highest HbA_{1c} (>8.5%) showed the highest morality, double-vessel, and triple-vessel disease compared to lower HbA_{1c} levels. We had similar outcomes in terms of mortality and trying to relate it to chronic glycemic control [19]. But this study had a follow up at four weeks and did not accurately measure the immediate outcome for elevated HbA_{1c} levels as our study did. We also did not find any statistically significant association between HbA_{1c} and mortality as this study did at the 4 week follow up. To detect myocardial perfusion defects and relate it to mortality a coronary angiography performed within 24 hours would have been a better predictor to relate it to plasma glucose, $HbA_{1c,}$ and mortality. Some studies used a different definition of DM control [14,15] as our study used HbA_{1c} above 7% as uncontrolled DM, while their study used 8.5%.

The limitations of our study were small sample size and limited number of outcomes. Out of a potential 2,204 patients with an AMI, only 202 had DM and HbA_{1c} measured within 24 hours of hospital admission. This affected the power of our study to detect an association. Since there was a low study population we completed a non-responder analysis based on whether HbA_{1c} was measured (Table three). The results indeed showed that the non-measured HbA_{1c} patients had different profile than those with measured HbA_{1c}. The patients with HbA_{1c} measured were statistically significantly different in terms of BMI>30 kg/m^2 (p-value 0.037), have COPD (p-value 0.031), and have insurance (p-value 0.010) In addition to small sample size we also had a limited number of outcomes. Out of the 202 patients in our study population, only 20 cases had complications. If a greater number of complications were found in a study population it could possibly change future management strategies for DM patients with AMI. Despite not measuring glucose levels, hyperglycemia could also affect mortality both acutely and chronically. Follow up HbA_{1c} levels should have been checked at monthly or yearly intervals to look for a possible association with mortality, as it might be a predictor of future mortality rather than short-term prognosis. Finally, we were not able to assess whether hypertension treatment or adecuate hypertension control was associated with mortality due to a lack of this particular information. Even though we did not find a statistically significantly increased risk of being classified as hypertensive, we are aware that due to the above mentioned limitation, no conclusions can be made in regard to a possible association between uncontrolled hypertension and mortality

5. Conclusion

In conclusion, our findings suggest that AMI patients with uncontrolled DM did not have an increased risk of mortality and cardiopulmonary complications compared to controlled DM. However, this needs further evaluation on a larger study population in order to give more accurate results evaluate DM patients. We recommend that all DM patients with an AMI should have HbA_{1c} measured to estimate their risk, manage patient's glycemic control better, and possibly prevent future complications from happening. In addition, other factors such as tobacco consumption, hyperlipidemia, obesity, and hypertension are important factors to be assessed and controlled for in order to improve survival in AIM."

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Statement of Competing Interests

The authors declare no competing interests.

List of Abbreviations

DM Diabetes mellitus, CAD coronary artery disease, MI myocardial infarction, CHD coronary heart disease, ADA American Diabetes Association, AMI acute myocardial infarction , T2DM diabetes mellitus type 2, WHO World Health Organization, ECG electrocardiogram, ICD international classification of diseases, BMI body mass index, COPD chronic obstructive pulmonary disease, REDCapTM (), OR odds ratio, HbA1c Glycosylated hemoglobin, A1C Glycosylated hemoglobin, IRB Institutional Review Board, FBG fasting blood sugar, GV variability glycemic, NSTEMI Non ST- segment elevation myocardial infarction, MACE Major adverse cardiovascular events, MAGE mean amplitude of glycemic excursions, IC confidence interval, MeSH medical subject headings, IDF International Diabetes Federation, ACS acute coronary syndrome, APG admission plasma glucose.

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