

The Association between Acute Heart Failure, Mortality and Duration of Type 2 Diabetes Mellitus in STEMI Patients

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Abstract: ***Background:** In patients with Type 2 Diabetes Mellitus, the decrease in insulin sensitivity predisposes for impaired myocardial structure and function and it partly explains the increased prevalence in Heart Failure in this population. The "Metabolic Memory", a phenomenon related to the prolonged harm produced by hyperglycemia, explains why macrovascular and microvascular damages continue despite intensive glycemic control in diabetics. Hyperglycemia in ST-Segment Elevation Myocardial Infarction (STEMI) worsens endothelial dysfunction, oxidative stress and vascular inflammation. This way, Type 2 Diabetes Mellitus (DM) patients with STEMI have a worse short-term prognosis than non-diabetics. There is limited information regarding the impact of DM duration on Acute Heart Failure (AHF) and mortality in patients with STEMI. **Aim:** This study aims at evaluating the development of Acute Heart Failure and mortality in STEMI patients and the impact of Diabetes Mellitus duration. **Methods:** We enrolled all Type 2 Diabetes Mellitus patients admitted with STEMI to the "Cardiac Intensive Care Unit" in UHC "Mother Teresa", Tirana, between September 2012 and September 2016 who presented in the first six to twelve hours of chest pain. Diabetic patients were divided in three groups: new onset, under treatment with oral antidiabetic drugs (OAD) and under treatment with insulin before admission, and we gathered data regarding glycemia at admission, smoking, age, gender, ethnicity, hypertension, type of Myocardial Infarction (MI), treatment method and we studied in-hospital Acute Heart Failure and mortality. **Results:** We enrolled 290 patients in total, out of which 67 (23.10%) had new onset DM, 161 (55.50%) were being treated with OAD and 62 (21.4%) were being treated with insulin. Total mortality was 15.20%. There was a higher mortality, although not statistically significant ($p=0.068$) in the insulin group (24.20%), compared to the new-onset group (10.40%) and OAD group (13.70%). Acute Heart Failure developed in 39% of cases in total and it was statistically significantly higher in the insulin group ($54.8\%/p=0.008$), compared to the new-onset group (40.30%) and OAD group (32.30%). **Conclusion:** Type 2 Diabetes Mellitus duration is an important factor in the short-term prognosis of STEMI patients regarding the development of Acute Heart Failure and mortality.*

Keywords: STEMI, diabetes mellitus duration, mortality, heart failure

1. Introduction

Type 2 Diabetes Mellitus (DM) and Cardiovascular Disease (CVD) develop simultaneously with metabolic abnormalities, causing changes in the vasculature. More than half of the mortality and a vast amount of morbidity in people with DM is related to CVD. Type 2 Diabetes Mellitus is characterized by a state of long-standing Insulin-resistance (IR), compensatory hyperinsulinaemia and varying degrees of elevated plasma glucose (PG), associated with clustering of cardiovascular risk and the development of macrovascular disease prior to diagnosis. Evidence supports the concept that hyperglycemia further decreases endothelium-derived Nitric-Oxide (NO) availability and affects vascular function mainly involving overproduction of reactive oxygen species (ROS) [1]. The latter influences on vascular dysfunction despite normalization of glucose levels. The phenomenon named "Metabolic memory" explains why macro- and microvascular complications progress, despite intensive glycemic control, in patients with DM, and in this process, ROS are particularly involved [2], [3]. In Type 2 DM patients, Insulin Resistance and hyperglycemia participate in the pathogenesis of a prothrombotic state [4]. Among factors contributing to the increased risk of coronary events in DM, platelet hyper-reactivity is of major relevance [5]. In patients with Type 2 DM, reduced insulin sensitivity

predisposes to impaired myocardial structure and function and partially explains the exaggerated prevalence of Heart Failure (HF) in this population. Together with Insulin Resistance, hyperglycemia contributes to cardiac abnormalities via ROS accumulation, AGE/RAGE signaling and hexosamine flux [6], [7]. Activation of ROS driven pathways affects coronary circulation, leads to myocardial hypertrophy and fibrosis with ventricular stiffness and chamber dysfunction [7]. That's why Type 2 DM patients with STEMI have a worse short-term prognosis than non-diabetics.

2. Literature Survey

Although there are a lot of trials which have studied the association between Diabetes Mellitus and the development of Acute Heart Failure (AHF) and Mortality, there is limited information regarding the impact of DM duration on AHF and mortality in patients with STEMI. This study aims at evaluating the development of Acute Heart Failure and mortality in STEMI patients associated to the duration of Type 2 Diabetes Mellitus.

3. Methods

3.1 Patients

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This is a prospective cohort study in which we enrolled all Type 2 Diabetes Mellitus patients admitted with STEMI to the “Cardiac Intensive Care Unit”, in UHC “Mother Teresa”, Tirana, between September 2012 and September 2016. All the enrolled patients presented in the first six to twelve hours of chest pain, and were treated in different manners, such as:

conservatively, with thrombolysis or with Primary PCI. Patients were divided in three groups: new onset Type 2 DM, under treatment with oral antidiabetic drugs (OAD) and under treatment with insulin before admission. We gathered patient characteristics such as glycemia at admission, smoking, age, gender, ethnicity, hypertension and white blood cells. (Table 1)

Table 1: Patient Characteristics

Variables	Type of Diabetes			Total (n=290)	p
	New-onset Diabetes Mellitus (n=67)	Diabetes Mellitus under insulin therapy (n=62)	Diabetes Mellitus under OAD (n=161)		
Sex (males)	47	36	122	205	0.034
	70.10%	58.10%	75.80%	70.70%	
Hypertension	35	49	109	193	0.005
	52.20%	79.00%	68.10%	66.80%	
Smoker	28	8	35	71	0.003
	41.80%	12.90%	21.70%	24.50%	
Ethnicity	62	58	154	274	<0.001
	92.50%	93.50%	95.70%	94.50%	
Heredity	1	3	21	25	0.009
	1.50%	4.80%	13.00%	8.60%	
Age	65.84±10.7	70.37±8.39	64.55±9.09	66.09±9.44	<0.001*
White blood cells (WBC)	11944.76±4937.89	12736.61±3358.13	11199.44±3766.13	11700.27±4023.09	0.032*
Glycemia at admission	317.91±110.73	295.85±112.12	274.99±121.62	289.37±118.13	0.039*

3.2 Definitions

Diagnosis of ST-Segment Elevation Myocardial Infarction: STEMI was defined according to the following criteria: 1) typical anginal chest pain > 20 min; 2) ST elevation at the J point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads; 3) detection of a rise and/or fall of cardiac biomarkers values.

Diagnosis of Heart Failure: The diagnosis of HF required at least two of the following criteria: 1) clinical signs or symptoms of congestive HF (pulmonary edema, crepitant rales, gallop rhythm, edema of the lower limbs, hepatomegaly, hepatojugular reflux, or jugular turgescence), 2) typical chest X-ray abnormalities, 3) left ventricular systolic dysfunction, or 4) the need for treatment with a digitalis, diuretic, ACE inhibitor, and/or inotropic agent. Both fatal and nonfatal Congestive Heart Failure (CHF) were considered in our study.

Diagnosis of Diabetes Mellitus was based on anamnestic data from the patient or family members in cases of known DM, and for the patients in whom DM was detected for the first time, we used the ADA/WHO diagnostic criteria.

Treatment of DM with high glycemic levels depended on patients conditions. Complicated patients with AHF, cardiogenic shock or extremely high glycemia were treated with insulin infusion, and stable patients were treated with subcutaneous insulin injections several times a day aiming at glycemic levels < 200 mg/dL.

3.3 Statistical Analysis

- For all categorical variables (nominal including binary/dichotomous, and ordinal) we calculated absolute numbers and corresponding percentages.
- For all numerical variables with normal distribution, we calculated arithmetic averages ± respective standard deviations.
- Random associations between variables were analyzed through binary logistic regression analysis.
- For each variable we estimated OD (odds ratio) and 95% confidence interval (CI).
- Differences between groups for discrete variables, were analyzed by Chi-Square test.
- Data was presented by simple and complex tables, as well as through graphics such as: bar-chart, box-plot, pie charts, etc.
- P was considered significant when ≤0.05. Data analysis was performed by statistical package SPSS (Statistical Package for Social Sciences) 20.0.

4. Results

We enrolled 290 patients in total, out of which 67 (23.10%) had new onset DM, 161 (55.50%) were being treated with OAD and 62 (21.4%) were being treated with insulin. (Figure 1)

The average age was 66.09±9.44 years, and the insulin group was of a statistically significantly older age 70.37±8.39 (p=0.001). (Figure 2)

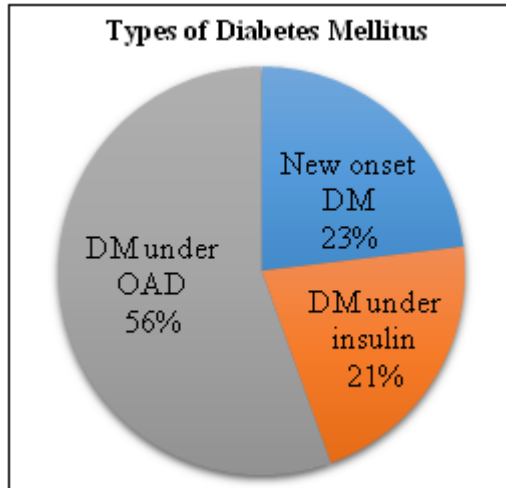


Figure 1: Types of Diabetes Mellitus

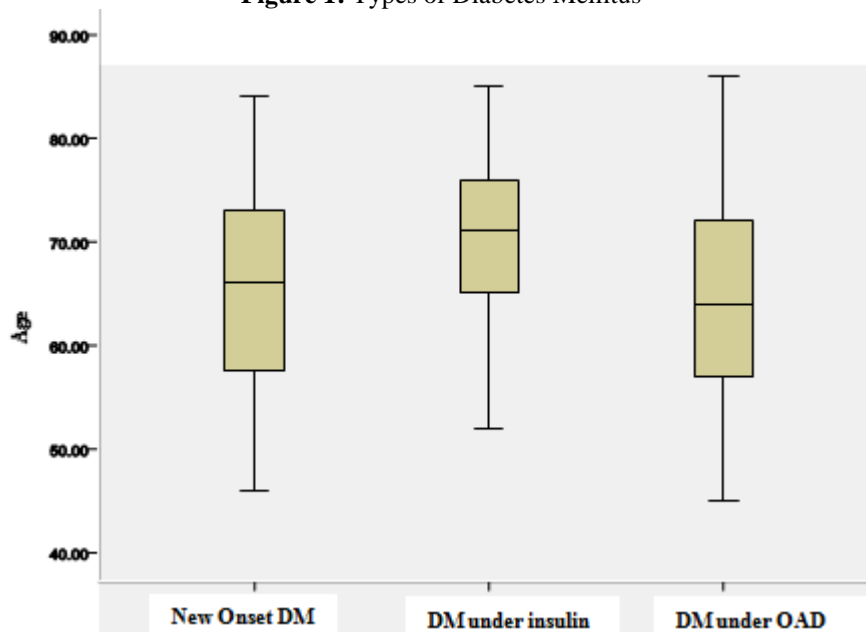


Figure 2: Age according to DM Type

Besides the older age in the insulin group, there was also a higher prevalence of hypertension (79%) in this group, compared to its prevalence in the new onset DM group and the OAD group, 52.20% and 66.80% respectively, which was statistically significant ($P=0.005$). 24.50% in the total group were smokers, 41.8% out of which had new-onset diabetes ($p=0.003$), whereas in the groups under insulin

therapy and OAD there were 12.90% and 21.70% smokers, respectively. The average glycemia at admission was 289.37 ± 118.13 mg/dL, and the new onset DM group had a statistically significantly higher glycemia 317.91 ± 110.73 mg/dl ($p=0.039$), followed by the insulin group with 295.85 ± 112.12 mg/dL, and the OAD group with 274.99 ± 121.62 mg/dL. (Figure 3)

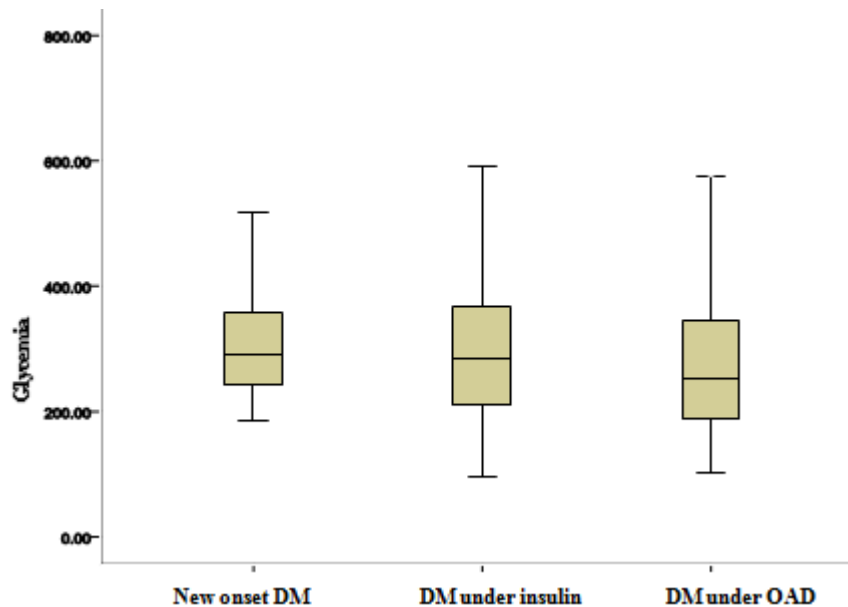


Figure 3: Glycemia according to DM Type groups

Total mortality was 15.20%. There was a higher mortality, although not statistically significant ($p=0.068$) in the insulin group (24.20%) compared to the new-onset group (10.40%) and OAD group (13.70%). Acute Heart Failure developed in

39% of cases in total and it was statistically significantly higher in the insulin group (54.8%/ $p=0.008$), compared to the new-onset group (40.30%) and the OAD group (32.30%). (Table 2)

Table 2: Patient Outcomes

Outcomes	Type of Diabetes			Total (n=290)	p
	New-onset Diabetes Mellitus (n=67)	Diabetes Mellitus under insulin therapy (n=62)	Diabetes Mellitus under OAD (n=161)		
Acute Heart failure	27	34	52	113	0.008
	40.30%	54.80%	32.30%	39.00%	
Death	7	15	22	44	0.068
	10.40%	24.20%	13.70%	15.20%	

5. Discussion

Epidemiological data indicate a greater risk of congestive heart failure (CHF) in diabetic patients compared to non-diabetic patients [8], [9]. DM is an important risk factor for mortality in patients with STEMI, regardless whether it is of new onset or under treatment. Various studies have come to the conclusion that regardless of the reperfusion therapy used such as thrombolysis, Primary PCI or even conservatory treatment, diabetic patients have higher rates of mortality [10]-[18]. It was also noticed that HF has a higher prevalence in diabetic patients compared to non-diabetics, [19]-[20] because DM is associated with myocardial structure and metabolic impairment which deteriorate cardiac dysfunction [21]-[27]. Our study confirmed that DM is a chronic condition leading to continuous damages of the myocardial structure and coronary arteries, regardless of insulin treatment. This was more obvious in the development of Acute Heart Failure, the prevalence of which was statistically significantly higher in the diabetic patients treated with insulin, who represent the group of patients with a longer duration of Type 2 DM. Mortality in the insulin group was as well higher than the other two groups, although it did not reach statistical significance. Of note there was no correlation between AHF and mortality with admission glycemia, which was statistically significantly higher in the new onset DM group compared to

the other two groups. This may be related to what we mentioned above, that a longer duration of DM leads to an increased risk for more serious and extensive coronary heart disease along with a more pronounced myocardial dysfunction [28]-[29].

This study had several limitations, including the inability to follow up Heart Failure and mortality for a longer period of time, which would give a clearer picture of the continuous damages from Diabetes, regardless of the normalization of glycemia values. HbA1c could not be routinely measured in patients with known diabetes, and thus we could not analyze this variable between groups to assess its impact. On the other hand we could not follow-up the systolic function in order to evaluate the systolic dysfunction in correlation with the duration of DM.

6. Conclusions

Despite the above-mentioned limitations, we think that this study has achieved its main goal regarding the evaluation of heart failure, by showing that the duration of DM, regardless of admission glycemia (which is known to be a predictive factor for bad short- and long-term prognosis), is an important prognostic factor in patients with DM and STEMI. As a conclusion, the duration of Diabetes Mellitus is an important element in the short-term prognosis of patients

with ST-Segment Elevation Myocardial Infarction regarding mortality and the development of heart failure.

7. Future Scope

Other trials are needed to better clarify the association between Diabetes Mellitus and the development of Acute Heart Failure and Mortality in STEMI patients, comparing diabetics to non-diabetics, and also comparing different treatment strategies. Future results with longer follow-up will assist in studying long-term differences in heart failure and mortality between different groups, and a routine measurement of the Left Ventricle systolic function would help to study an association between hyperglycemia and a decrease in systolic function.

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