Original Article
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Impact of Glycemic Status on Left Ventricular Systolic Function in Patients with Acute Coronary Syndrome

Alaaeldin Abdelhady Amin **Waleed Abdelsalam Ammar** **Azza Abdelmoniem Farrag**

Cairo University Hospitals, Department of Cardiovascular Medicine, Cairo, Egypt

Background: Diabetes mellitus (DM) and left ventricular systolic dysfunction (LVSD) commonly coexist; increasing morbidity and mortality. The aim of this study is to detect the correlation between glycemic status of patients presenting by acute coronary syndrome (ACS) and left ventricular global and regional systolic function.

Method: The study included 510 patients presenting by ACS and referred for coronary angiography. In addition to routine laboratory tests, Glycated hemoglobin (HbA1C) level, as a marker of chronic glycemic status, was measured. Every patient was subjected to transthoracic echocardiographic study with accurate evaluation of left ventricular systolic function by both m-mode and biplane Simpson's method, in addition to calculation of regional wall motion score index (RWMSI). The whole study population was divided into two groups; diabetic and non-diabetic based on cutoff point of HbA1C value 6.5%. The non-diabetic group was subdivided into two groups; high risk and low risk based on cutoff point of HbA1C value 5.7%.

Results: Sixty four percent of the studied population had DM. The mean HbA1C level was 7.6±2.2%. The mean left ventricular ejection fraction (LVEF) was 54±11 and mean RWMSI was 1.3±0.3. There was significant negative correlation between the HbA1C level and the LVEF (r= -0.101, p<0.022). There was significant positive correlation between HbA1C level and RWMSI (r=0.109, p<0.014). The non-diabetic high risk group had lower LVEF and higher RWMSI than the low risk group (p<0.041 and p<0.002 respectively).

Conclusion: Chronic hyperglycemia in patients with uncontrolled DM may be a risk factor for developing LVSD in patients presenting by ACS. Glycated hemoglobin level may predict LVSD in patients with ACS. Non-diabetic patients who are at higher risk of developing DM have higher incidence of LVSD.

Key words: Diabetes mellitus, glycated hemoglobin, ejection fraction, acute coronary syndrome

Introduction

Cardiovascular diseases (CVD), including heart failure and coronary artery disease (CAD), are the major causes of morbidity and mortality in patients with type 2 diabetes mellitus (DM) (1,2). Diabetic patients usually present several factors contributing to the risk of CVD, which include hyperglycemia, insulin resistance, dyslipidemia and hypertension (1).

Apart from CAD as a major determinant of cardiomyopathy in diabetic patients, several studies demonstrated other pathophysiological mechanisms that alter the cardiac structure and promote myocardial fibrosis. These mechanisms include changes in free acid metabolism, increased oxidative stress, apoptosis and activation of the renin-angiotensin system (3).

Corresponding Author: Alaaeldin ABDELHADY AMIN; Kasralainy Hospital, Cardiovascular Medicine, Alsaraya St, Cairo, Egypt. **E-mail**: *alaaeldin.a.mahmoud@kasralainy.edu.eg*

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The contribution of these factors to left ventricular systolic dysfunction (LVSD) in patients with CAD remains unclear. Glycated hemoglobin (HbA1C) level reflects the average blood glucose concentrations over a period of two to three months. The measurement of HbA1C is well standardized with less biologic variability than fasting and postprandial plasma glucose levels. It is considered a marker of chronic glycemic status and used for monitoring efficacy of antidiabetic medications (4).

The relationship between HbA1C and CVD remains controversial (5). In ARIC study; HbA1C values showed a J-shaped association with the incidence of heart failure (6). Even among non-diabetics, the prediabetic state has been demonstrated to increase the risk for LVSD (7, 8).

In the present study, we examined the correlation between the level of HbA1C and left ventricular systolic function in both diabetic and non-diabetic patients at time of presentation by an acute coronary syndrome (ACS).

Study Design

The study population included 510 patients presenting by an ACS to four tertiary centers over a period of one year. All patients were subjected to medical history taking and clinical examination. Cardiovascular risk factors as smoking, DM, hypertension, obesity and family history of CAD were reported. The study protocol was approved by the local ethics committee.

All patients presenting by an ACS fulfilling any of the following criteria were included in the study: Typical anginal symptoms, electrocardiographic changes suggestive of ischemia, echocardiographic evidence of segmental wall motion abnormalities, Positive cardiac biomarkers and angiographic evidence of CAD.

Blood samples were taken at the time of admission for HbA1C, serum creatinine in addition to other routine laboratory measurements. Samples for fasting plasma glucose (FPG) were taken after eight hour fast. Glycated hemoglobin level was assessed quantitatively using Siemens Dimension Xpand Plus assay and results were reported as percentage of total hemoglobin.

The diagnosis of DM was based on the recent American Diabetes Association (ADA) recommendations for classification and diagnosis of DM [9]. The criteria used for diagnosis were: FPG ≥126 mg/dL (7.0 mmol/L) and/or HbA1C ≥ 6.5%. If the two tests were concordant for the diagnosis of DM, additional testing was not needed. If the two tests were discordant, the test that was diagnostic of DM was repeated on the next day to confirm the diagnosis.

Diabetic patients were classified into controlled and uncontrolled groups based on the cutoff point of HbA1C value 7%. While non-diabetic patients were classified as low and high risk groups for development of DM based on cutoff point of HbA1C value 5.7%.

Transthoracic echocardiography

Left ventricular internal dimensions and wall thickness were measured through standard parasternal short axis view using M-mode pattern (10). Left ventricular ejection fraction (LVEF) was measured using biplane Simpson's method (10) in the apical four chamber and apical two chamber views. Simpson's algorithm divides the left ventricle into a series of stacked oval disks and the volume of the entire left ventricle can be derived from the sum of the volume of the individual disks through a formula integrated within the software package of the echocardiographic machine (*Figure-1*).

Qualitative assessment of the segmental wall motion abnormalities at rest was done. Each myocardial segment was given a score as follows: 1 for normal contraction or hyperkinesia, 2 for hypokinesis (reduced thickening), 3 for akinesia (absent or negligible thickening as scar), 4 for dyskinesia (systolic thinning or stretching including aneurysmal segments). Regional wall motion score index (RWMSI) was then calculated as sum of all scores divided by the number of segments visualized. The echocardiographic machine used was Philips ultrasound system (IE33, Best, Netherlands). All measurements were reported as per American Society of Echocardiography (ASE) guidelines and recommendations (10).

Statistical analysis

All statistical analyses were performed using SPSS for windows with statistical package version 18. Normally distributed continuous variables were represented as mean ±SD, or as the percentage of the sample. Fisher's exact test will be used to determine differences in patient characteristics.

Comparison between diabetic and non-diabetic groups was done using two-tailed unpaired student t test for continuous variables and the Pearson's chi-square test for categorical variables. Correlations between normally distributed variables were done using Pearson correlation coefficient. A p value < 0.05 was considered significant for all tests.

Results

Baseline clinical characteristics, laboratory and echocardiographic data of the whole study participants are listed in *Table-1* and *Table-2*. Male gender presented 85.1% of the sample. Baseline clinical characteristics, laboratory and echocardiographic data of diabetic and non-diabetic groups are listed in *Table-3* and *Table-4*. Both diabetic and non-diabetic groups had comparable gender distribution, prevalence of obesity and clinical presentation. However, diabetic patients were older and had more prevalence of hypertension.

The majority of diabetic patients (71%) had poorly controlled DM. Diabetic patients had high levels of HbA1C and FPG at time of presentation for coronary angiography (Mean values: 8.6±2.2 and 145±42, respectively). They also had lower HDL cholesterol and lower creatinine clearance (p = 0.014 and p=0.002, respectively). Diabetic patients had higher RWMSI in comparison with non-diabetic patients (p = 0.033).

Table-1: Baseline clinical characteristics of the participants

Variables	Patients *(n:510)*
Age	57 ±10
Gender	
- Male (%)	434 (85.1)
- Female (%)	76 (14.9)
Risk Factors	
- DM	328 (64.3)
- Duration DM (in years)	6 ±8
- Treatment of DM (n=328)	
OHD (%)	118 (36%)
Insulin (%)	89 (27.1)
Combined therapy (%)	56 (17.1)
Diet (%)	65 (19.8)
- HTN	293 (57.5)
- Duration HTN (in years)	6 ±7
- Current smoker (%)	287 (56.3)
- Smoking (in years)	21 ±15
Obesity	
- BMI (cm)	30 ±3
- WC (cm)	100 ±9
- WHtR (cm)	0.6 ±0.1
Clinical Presentation	
- Unstable angina (%)	220 (43.1)
- NSTEMI (%)	137 (26.9)
- STEMI (%)	153 (30)

Abbreviations: OHD: oral hypoglycemic drugs, DM:diabetes mellitus, HTN: Hypertension, BMI: Body mass index, WC: waist circumference, WHtR: waist height ratio, NSTEMI: Non ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction.

Baseline clinical and echocardiographic data of low risk and high risk non-diabetic patients are listed in Table 5. High risk non-diabetic patients had significantly lower LVEF and higher RWMSI (p=0.041 and p=0.002 respectively). There was negative correlation between HbA1C level and LVEF (r= -0.101, p<0.022)(*Figure-2*). There was positive correlation between HbA1C and RWMSI (r= 0.109, p<0.014)(*Figure-3*).

Table-2: Baseline Laboratory and echocardiographic data of the whole study participants

Variables	Patients *(n:510)*
Laboratory data	
- FPG (mg/dl)	127.5 ±41.6
- HbA1c (%)	7.6 ±2.2
- TC (mg/dl)	197.3 ±47.6
- TGs (mg/dl)	172.9 ±78.9
- HDL (mg/dl)	35.1 ±12.8
- LDL (mg/dl)	139.3 ±269.9
- Creatinine (mg/dl)	1.13 ±0.613
- CrCl	77.39 ±29.33
Echocardiographic data	
- LVEF	54 ±11
- RWMSI	1.3 ±0.3

Abbreviations: FPG: Fasting plasma glucose, HbA1c: Glycated Hemoglobin level, TC: Total cholesterol, TGs: Triglycerides, HDL: High density lipoproteins, LDL: Low density lipoproteins, CrCl: Creatinine clearance, LVEF: Left ventricular ejection fraction, RWMSI: Regional wall motion score index.

Table-3: Baseline clinical and demographic characteristics of diabetic and non-diabetic groups

Variables	DM *(n:328)*	Non-DM *(n:182)*	*p*
Age	57 ±9	55 ±10	0.013
Male (%)	274 (83.5)	160 (87.9)	0.184
Risk factors			
- HTN (%)	222 (67.7)	71 (39)	<0.001
- HTN (years)	7 ±7	3 ±5	<0.001
- Obese (%)	157 (46.9)	73 (40.1)	0.154
Obesity parameters			
- BMI (Cm)	30.072±3.16	29.195 ±3.34	0.003
- WC (Cm)	100 ±9	100 ±10	0.393
- WHtR	0.59 ±0.057	0.58 ±0.057	0.397
Clinical presentation			
- Unstable angina (%)	138 (42.1)	82 (45.1)	NS
- NSTEMI (%)	99 (30.2)	38 (20.9)	
- STEMI (%)	91 (27.7)	62 (34.1)	

Abbreviations: HTN: Hypertension, BMI: Body mass index, WC: waist circumference, WHtR: waist height ratio, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction.

Table-4: Laboratory and echocardiographic data of diabetic and non-diabetic groups

Variables	DM	Non-DM	*p*
Laboratory data			
- FPG (mg/dl)	145 ±42	96 ±13	<0.001
- HbA1c (%)	8.6 ±2.2	5.8 ±0.5	<0.001
- TC (mg/dl)	199 ±48	200 ±46	0.342
- TGs (mg/dl)	177 ±80	164 ±76	0.069
- LDL (mg/dl)	126 ±41	162 ±448	0.15
- HDL (mg/dl)	34 ±8	37 ±18	0.014
- Creatinine (mg/dl)	1.2 ±0.701	1 ±0.381	<0.001
- CrCl	74.4 ±30.6	82.8 ±26.1	0.002
Echocardiography			
- LVEF	53 ±12	55 ±10	0.085
- RWMSI	1.302 ±0.34	1.23±0.308	0.033

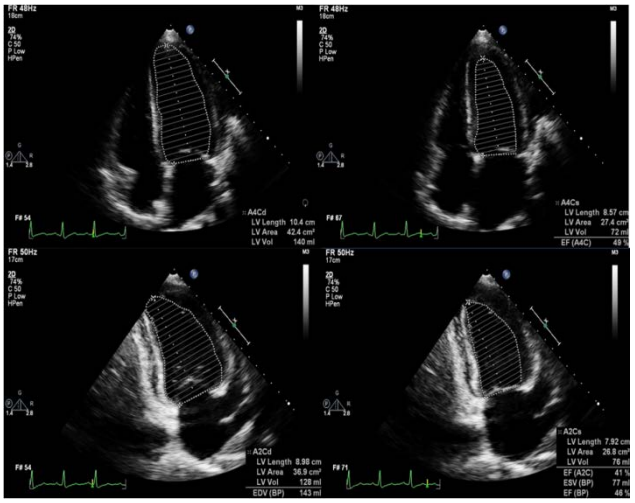
Abbreviations: FPG: Fasting plasma glucose, HbA1c: Glycated Hemoglobin level, TC: Total cholesterol, TGs: Triglycerides, HDL:High density lipoproteins, LDL: Low density lipoproteins, CrCl: Creatinine clearance, LVEF: Left ventricular ejection fraction, RWMSI: Regional wall motion score index.

Table-5: Clinical and echocardiographic data of low risk and high risk non-diabetic patients

Variables	High risk *(n:112)*	Low risk *(n:70)*	*p*
Age	55 ±10	55 ±10	0.947
Male (%)	99 (88.4)	61 (87.1)	0.818
Current smoker (%)	80 (71.4)	39 (55.7)	0.095
Obese (%)	53 (48.4)	20 (28.6)	0.065
BMI (Kg/m^2)	30 ±3.4	29 ±3.3	0.059
WC (Cm)	100 ±10	98 ±9	0.133
WHtR	0.6 ±0.1	0.6 ±0.1	0.252
LVEF	54 ±11	57 ±10	0.041
RWMSI	1.29±0.32	1.14±0.25	0.002

Abbreviations: BMI: Body mass index, WC:Waist circumference, WHtR:Waist height ratio, LVEF:Ejection fraction, RWMSI: Regional wall motion score index.

Figure-1: Left ventricular ejection fraction by biplane Simpson's method. Upper panel shows apical 4 chamber view while lower panel shows apical two chamber view (end-diastolic and end-systolic frames).



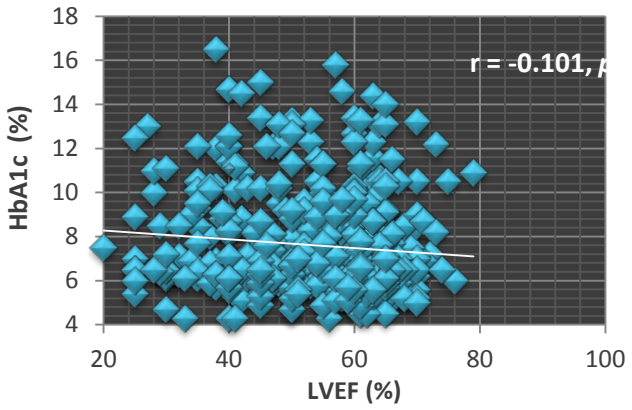


Figure-2: Correlation between HbA1c level and LVEF

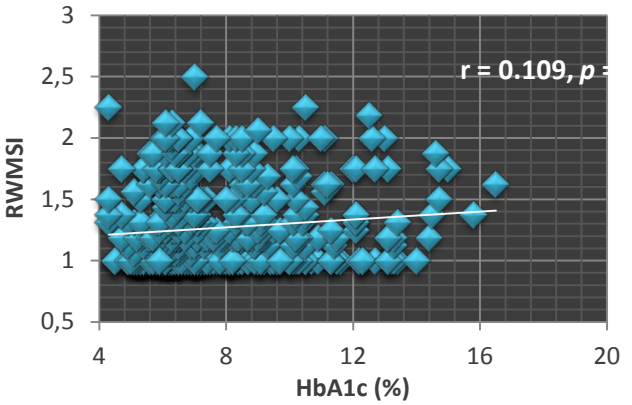


Figure-3: Correlation between HbA1c level and RWMSI

Discussion

Several studies demonstrated a clear association between DM and left ventricular dysfunction even in absence of significant CAD. Most of these studies emphasize the presence of left ventricular diastolic dysfunction and increased LV filling pressure. Tsai JP et al (11) study recently recruited 142 patients with first incidence of STEMI. The study concluded that HbA1C is independently associated with impaired LV diastolic function and increased filling pressures after STEMI. In a cross sectional study of 100 patients with newly diagnosed type 2 DM, Sanjeev Kumar et al (12) reported a significant positive correlation between HbA1C and presence of left ventricular diastolic dysfunction (p=0.0157).

Few studies however examined the association between glycemic status and LVSD. The level of HbA1C is used as a target of glycemic control to reduce microvascular complications; however its correlation with CVD is not well established. In the present study, the HbA1C level was significantly correlated with the LVEF as an important parameter of global left ventricular systolic functions.

In a recent study (13), a linear decrease in LVEF was found with raised level of HbA1C in patients presented with unstable angina, STEMI and NSTEMI (p=0.0043, p=0.029 and p=0.0015 respectively). Patients with HbA1C value ≥ 6.5% had significantly lower LVEF compared with those of lower values (p=0.0001). In the present study, we included a larger number of patients (510 vs. 50 patients) and there was no significant difference in LVEF between diabetic and non-diabetic groups (based on cutoff point of HbA1C value 6.5%).

Another study conducted by Mayorga et al (14) included patients with type 2 DM and first incidence of acute myocardial infarction. Glycated hemoglobin levels above 8.5% had a tendency to present with LVEF below 50% (p : 0.019). Our study included a larger number of diabetic patients (328 vs. 36 patients) and there was no significant difference in LVEF between controlled and uncontrolled diabetic patients (based on cutoff point of HbA1C value 7%).

Isabelle Pham et al (15) conducted a study to assess the prevalence of subclinical diabetic cardiomyopathy occurring among diabetic patients. The study included 656 asymptomatic patients with type 2 DM and patients with CAD represented 11.1% of the study participants. Multivariate logistic regression analysis showed that HbA1C is an independent predictor of LVSD (OR 1.9; CI [1.1–3.2], $p < 0.05$). In the present study, diabetic patients were symptomatic and presented by an ACS. The subclinical alterations of cardiac structure and function might have an impact on the negative correlation between HbA1C level and LVEF at time of presentation.

Even among non-diabetic patients, a study (16) of 200 patients presenting with ACS demonstrated a linear correlation between LVEF and HbA1C (p= 0.019). In our study, high risk non-diabetic patients had lower LVEF than low risk patients. Dan E. Høfsten et al (17) study included 203 patients with impaired glucose tolerance and presenting by an acute myocardial infarction. After adjustment for confounding variables; including hypertension and dyslipidemia; a statistically significant linear correlation was observed between the degree of dysglycemia and LVEF (p=0.03). The impact of glycemic level on LVEF appears to be a continuum across the entire spectrum of sub-diabetic glycemic values.

Regional wall motion score index (RWMSI) reflects regional LVSD and correlates well with LVEF. Although not routinely measured, RWMSI can predict the severity of CAD. To our knowledge, the correlation between HbA1C level and RWMSI was not previously studied. In the present study, we demonstrated a significant positive correlation between both parameters (r :0.109, p<0.014). Both diabetic and high risk non-diabetic patients had higher RWMSI. This further emphasizes the impact of glycemic status on both left ventricular function as well as the coronary artery affection.

Conclusion

Chronic hyperglycemia in patients with uncontrolled DM may be a risk factor for developing LVSD in patients presenting by ACS. Glycated hemoglobin level may predict LVSD in patients with ACS. Non-diabetic patients who are at higher risk of developing DM have higher incidence of LVSD.

Study limitations

All patients included in the study had evidence of CAD. The extent of regional and global LVSD might have been correlated with the extent of coronary artery affection. The pure impact of glycemic status on LVSD could not be ruled out.

Conflict of Interest

The authors declare that no conflict of interest exists in publishing this article.

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