

ORIGINAL ARTICLE

Does the Admission HB1c Level Have an Impact on the Size of Myocardial Infarction and Residual Viability in Type II Diabetics Surviving Their 1st Myocardial Infarction?

Rayan M, MD.

Department of cardiology, Ain shams University

Background	Hyperglycemia is strongly associated with increased mortality in type II diabetic patients, hence, the simple message used to be "The lower, the better." But, the release of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) data cast doubt on this and has provoked deliberation ever since. The trial was halted prematurely because of an increased risk of death in patients who underwent intensive blood glucose lowering.
Methods	We included 300 patients with type II diabetes who survived their 1 st time myocardial infarction who were kept on the same type of medication Only patients, who received thrombolytic therapy and were maintained on the same antidiabetic therapy for at least 3 months before the infarction, were included. Assessment for other risk factors was done to all included patients such as gender, hypertension, smoking and dyslipidemia. Infarction size and residual viability were assessed using rest–Trimetazidine Tc99m Sestamibi SPECT imaging.
Results	we found a bimodal U shaped behavior of glycated hemoglobin, where the extremely high and low levels of Hb1c were associated with large infarction size as compared to middle levels. And that high LDL levels was strongly associated with larger size of infarction and less viability. Other risk factors did not show a strong influence on the infarction size or viability.
Conclusions	we concluded that extremely over or under control of blood glucose ,as reflected by HB1c level, is associated with increased infarction size and reduced residual viability and that optimal therapy for diabetics should address not only glycemic control, but also the coexisting risk factors especially LDL levels.
Keywords	Hb1c, infarction size, viability, Tc99m Sestamibi (Heart Mirror J 2009; 3(2): 76-79)

INTRODUCTION

hyperglycemia during acute myocardial infarction is associated with a poor prognosis .In acute coronary syndrome, glucose metabolism is modified, and stress hyperglycemia commonly occurs (1). Epidemiological studies showed a relationship between glycated hemoglobin levels and cardiovascular events in patients with type II diabetes as it is a measure of the mean blood glucose level during the previous 2 to 3 months. One of the most important questions in diabetes management is whether long term glycemic control can reduce the risk of cardiovascular diseases. This question was supported by findings from some but not all previous clinical trials (2).

METHODS

we included 300 consecutive type II diabetic patients who had first time anterior myocardial infarction and were referred to the nuclear cardiology unit of Ain-Shams University throughout the period from June 2007 to June 2009 for the assessment of residual viability. The diagnosis of 1st time myocardial infarction was defined according to the European society of cardiology and American college of cardiology criteria (3):

1. Typical anginal chest pain of more than 30 minutes duration.
2. Typical ST segment elevation of 1 mm or more in anterior leads pathognomonic of acute myocardial infarction.

Abbreviations and Acronyms

HB1c : glycated hemoglobin
 LDL : low density lipoprotien

3. A rise of cardiac enzymes CPK and its MB fraction more than twice the normal levels.

Only patients, who received thrombolytic therapy and were maintained on the same antidiabetic therapy for at least 3 months before the infarction, were included.

Exclusion criteria:

Patients with type I diabetes (Based on peptide c assay) and those with previous myocardial infarction (Based on history, pathological Q waves) were excluded from the study. The included patients underwent the following. A full detailed history was taken from all patients for duration of DM, type and dose of therapy taken, history of chest pain and previous admission to coronary care unit. Other risk factors such as hypertension, smoking, and dyslipidemia were examined. Height and weight to calculate body mass index, where obesity was diagnosed if BMI >30 kg/m2. It was calculated online <http://www.mcw.edu/calculators/bodymassindex.htm>. A 12 lead ECG was obtained to document the presence of anterior myocardial infarction and to exclude patients with left bundle branch block. HB1c and lipid profile were obtained within 3 hours of hospital admission.

Rest Technium 99 m Sestamibi scan using Trimetazidine adopted by our lab was applied to all patients. A dose of 15-20 mCi of Tc 99 m was given at rest after the ingestion of 140 mg of Trimetazidine taken as 70 mg on 2 divided dose the day before the test and 70 mg as a single dose 2 hours before the injection of the radiotracer. GE Starcam 4000i gamma camera equipped with a low energy all purpose collimator was used. an arc of a 180° was used, spanning from 45° right anterior oblique to 45° left posterior position. Thirty two projections each of 20 seconds were acquired in stop and shoot mode over a 180° arc on 64x64 matrix with photon energy limits set at 20% window around 140 KeV Tc 99 m peak. Processing and reconstruction were performed using standard back projection algorithms and a Ramp-Henning filter. Trans axial image reconstruction and analysis was performed to estimate infarction size and the residual viability. in order to express the % of infarcted myocardium, A five point scale, with the score representing the reduction of the radiotracer uptake (0=normal uptake, 1=slight reduction or equivocal (<60% uptake), 2=moderate reduction (40-60% uptake) 3=severe reduction (20-40% uptake), 4=absent uptake (0- >20% uptake) was applied to the 17 segment myocardial (4). A summed rest score (SRS) was normalized to the maximum score (17x4=68) and multiplied by 100. Defects 5-9% were considered mild or small defects, 10-14% were moderate and >15% were considered large defects.

Theoretically, attenuation of counts caused by huge breast may cause defects below the 60% threshold, which would erroneously be labeled as infarction (5). Defects <5% are trivial or small in size and are usually considered normal finding especially if confined to apical cuts (6). The residual viable tissue was estimated by the percent of Tc99m uptake, within the infarcted area, compared to normal segments (7).

Statistics

all data were collected, tabulated and analyzed using Microsoft excel 2003 and online graph Pad QuickCalcs. Data are expressed as percentage or mean and SD. Student t test, one-way ANOVA (with post hoc test) were used to compare two or more groups respectively. Linear and multiple regression analysis with Pearson’s coefficient were used to assess the strength of association between variables. P value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical data of the study group are summarized in (Table 1).

Table 1: Demographic and clinical data of the studied group:

Variable	N=300
Age in years m±SD	54±6.2
Gender	251
male n (%) / female n (%)	(84%) / 49(16%)
Hypertension n (%)	171 (57%)
Smoking n (%)	233 (77.7%)
BMI>30 n (%)	67 (22%)
Duration of DM m±SD years	3.2±1.2
Insulin/Oral n (%)	85(28%) / 215(72%)
LDL mg%	149.9±32.7
Total triglycerides mg%	237.9±57.4

M stands for mean, n stands for number.

Based on the level of admission HB1c, Patients’ data were categorized into 4 subgroups. *Group (1):* it included 17 patients with HB1c <6% with a mean level of 5.6±0.2. *Group (2):* it included 113 patients with hb1c >6-8.4% with a mean level of 7.3±0.8. *Group (3):* it included 118 patients with hb1c >8.4-12% with a mean level of 9.8±0.98. *Group (4):* it included 52 patients with hb1c >12% with a mean level of 12.89±0.45. The four subgroups were comparable as regards demographic and clinical data. infarction size and radiotracer uptake showed a highly significant difference between the 4 subgroups with the a moderate to large defects with reduced radiotracer uptake were observed in group 1 and 4 as shown in (Table 2).

Table 2: Demographic, clinical and TC99m results in the 4 subgroups:

Variable	Group1 (17)	Group2 (113)	Group3 (118)	Group4 (52)	P value
Age	55±5.4	55±6.7	54±6	54±5.9	p>0.05
Gender M/F	16(94%)/1(6%)	91(81%)/22(19%)	97(82%)/19(18%)	45(86.5)/7(13.5)	
Duration DM	2.9±1.3	3.2±1.2	3.3±1.2	3.4±1.2	p>0.05
Insulin/Oral	10/7	39/74	24/94	12/40	p>0.05
Hypertension	8 (44.4%)	62 (54.9%)	59 (50%)	42 (80.8%)	p>0.05
Smoking	12 (66.7%)	87 (76.9%)	92 (77.9%)	42 (80.8%)	p>0.05
BMI >30	4 (23.69%)	25 (21.2%)	25 (21.2%)	13 (25%)	p>0.05
LDL	142.9±29.3	148±26.7	151.7±32.4	153.6±31.7	p>0.05
Triglycerides	230.9±57.6	235.7±52.3	241.9±58.4	236.4±57.5	p>0.05
% of myocardium	14.6±4.12	8.3±2.16	9.8±3.12	12.2±4.10	P<0.001
Radiotracer	30±10.12	66±16.16	56±13.16	40±14.09	P<0.001

The correlation between infarction size and different risk factors were analyzed. It showed that admission Hb1c showed a significant positive correlation with infarction size ($r=0.15$, $p < 0.01$) and a highly significant negative correlation with radiotracer uptake in the area of infarction ($r=-0.22$, $p < 0.001$). Also, the level of LDL showed a significant positive correlation with size of the infarction and a significant negative correlation with the degree of radiotracer uptake as shown in (Table 3).

Table 3: the correlation between different risk factors and infarction size and residual viability:

variable	R value	P value
Infarction size and Hb1c level	0.15	<0.001
Radiotracer uptake and Hb1c level	-0.22	<0.001
Infarction size and triglyceride level	0.08	>0.05
Radiotracer uptake and triglyceride level	-0.09	>0.05
Infarction size and LDL level	0.21	<0.001
Radiotracer uptake and LDL level	-0.21	<0.001

DISCUSSION

Elevated glucose is not only a symptom of glucose dysregulation, but also of stress and a more high-risk patient population. HbA1c is an easy marker of long-term glucose regulation and elevated HbA1c was associated with increased cardiovascular risk in patients with or without diabetes (8). In the present study, we found a U shaped behavior associated with admission HB1c, where the extremely low (Mean 5.6%) and the extremely high levels (Mean 12.98%) were associated with a moderate to large infarction size and less residual viability as compared with moderate levels (Mean 7.3-9.8%). Timmer, et al. (9) reported that high admission glucose levels even in non-diabetic patients treated with thrombolytic was associated with significantly larger infarction size. Also, Cakmak, et al. (10) found that an elevated glycated hemoglobin

level on admission was associated with higher ischemic scores and mortality. This was explained by the increased thrombotic properties of platelets in a hyperglycaemic environment. Furthermore, elevated glucose levels are accompanied by increased levels of free fatty acids (FFA) which may increase infarct size, compromise myocardial performance during acute coronary syndromes and reduce endothelium-derived vasodilatation in myocardial tissue limiting myocardial reperfusion (11). On the other hand, Doubts have been casted on the simple message that used to be "The lower, the better", by the release of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) data. The trial was halted prematurely because of an increased risk of death in patients who underwent intensive blood glucose lowering. Unexpectedly, the ACCORD study (12) showed a 22% ($p=0.04$) relative increase in total mortality in the intensive glucose lowering arm. To date, there is no clear explanation for the higher mortality in ACCORD. In ACCORD, severe hypoglycaemia requiring medical assistance was three times more common in the intensive group (10.5% and 3.5% respectively). It is plausible that severe hypoglycaemia may possibly have triggered fatal cardiac events such as ventricular arrhythmias particularly in those with compromised cardiac function and established autonomic neuropathy (13). An adverse cardiovascular outcome was not seen in the ADVANCE group (14) who had generally better glycemic control at the start of the study and who had a more gradual lowering of glucose during the study. Severe hypoglycaemia was less frequent than in ACCORD. In the present study, high LDL level was one of the independent factors increasing the size of infarction and decreasing residual viability. This is supported by the study of Cakmak, et al. (10) who found a significant correlation between high LDL levels and total ischemic burden in patients with type 2 diabetes. Oxidized LDL is thought to play a key role in the inflammatory process associated with the atherosclerotic disease progression in vessel walls. At reasonable blood

levels, LDL can pass in and out of the intima. In excess, LDL particles tend to get stuck in the matrix and subjected to oxidation. Oxidative changes of LDL particles are recognized by the cells as foreign and the immune system is activated. Meisinger, et al. (15), found that the level of oxidized LDL was the strongest predictor of CHD events compared to a conventional lipoprotein profile and other traditional risk factors for CHD. On the other hand, in our work, other risk factors such as male gender, obesity, hypertension, smoking, triglyceride level did not show any significant correlation with the size of infarction or residual viability. This is supported by the study of Pingitor, et al. (16) and the study of Cakmak, et al. (10) who found that Infarct size was not influenced by patient age, gender, history of arterial hypertension, hypertriglyceridaemia, obesity nor tobacco smoking.

CONCLUSION

our results demonstrated that extremely low or high HB1c levels was associated with increased infarction size and reduced residual viability .in the light of these findings, appropriate target should be adjusted for each patient with regular assessment for severe hypoglycemic episodes and hypoglycemia unawareness and, optimal therapy for people with diabetes should include not only glycemic control, but also other coexisting risk factors such as lipid abnormalities.

Corresponding Author

Prof. Mona Rayan
Ainshams university; Cardiology Department
E-mail: braveear58@yahoo.com

REFERENCE

1. Husband DJ, Alberti KG, Julian DG. "Stress" hyperglycaemia during acute myocardial infarction: An indicator of pre-existing diabetes? *Lancet* 1983; 2(8343):179-81.
2. Goff DC,Jr, Gerstein HC, Ginsberg HN, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: Current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol* 2007; 99(12A):4i-20i.
3. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36(3):959-69.
4. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Int J Cardiovasc Imaging* 2002; 18(1):539-42.
5. Berman DS, Abidov A, Kang X, et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. *J Nucl Cardiol* 2004; 11(4):414-23.
6. Miller TD, Christian TF, Hopfenspirger MR, et al. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. *Circulation* 1995; 92(3):334-41.
7. Beller GA. Noninvasive assessment of myocardial viability. *N Engl J Med* 2000; 343(20):1488-90.
8. Rasoul S, Ottervanger JP, Bilo HJG, et al. Glucose dysregulation in nondiabetic patients with ST-elevation myocardial infarction: Acute and chronic glucose dysregulation in STEMI. *Neth J Med* 2007; 65(3):95-100.
9. Timmer JR, Van Der Horst ICC, Ottervanger JP, et al. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J* 2004; 148(3):399-404.
10. Cakmak M, Cakmak N, Cetemen S, et al. The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. *Can J Cardiol* 2008; 24(5):375-8.
11. Lind L, Fugmann A, Branth S, et al. The impairment in endothelial function induced by non-esterified fatty acids can be reversed by insulin. *Clin Sci (Lond)* 2000; 99(3):169-74.
12. Friedewald WT, Buse JB, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358(24):2545-59.
13. Dhar GC. Intensive glycemic control: Implications of the ACCORD, ADVANCE and VADT trials for family physicians. *Can Family Phys* 2009; 55(8):803-4.
14. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358(24):2560-72.
15. Meisinger C, Baumert J, Khuseynova N, et al. Plasma oxidized low-density lipoprotein, a strong predictor for acute coronary heart disease events in apparently healthy, middle-aged men from the general population. *Circulation* 2005; 112(5):651-7.
16. Pingitore A, Di Bella G, Lombardi M, et al. The obesity paradox and myocardial infarct size. *J Cardiovasc Med* 2007; 8(9):713-7.