

The Role of Hba1c In Severity and Mortality Rate of St Segment Elevation Myocardial Infarction For Hospitalized Libyan Non Diabetic Patients

Asgad Abdalgar^{1,2*} and Hanan K .G. Altalhi¹¹Faculty Of Medicine University Of Omar El Mukhtar Albayda - Libya²Faculty Of Medical Technology University Of Omar El Mukhtar Albayda - Libya***Corresponding author:**

Asgad Abdalgar

Received: 21.10.2019**Accepted:** 07.11.2019**Published:** 28.12.2019

Abstract: Background:The severity of coronary artery disease (CAD) is directly related to the quality of glucose control in diabetic patient. Additionally diabetes is associated with increased mortality following acute myocardial infarction compared to general population. **Objectives:**To evaluate the association of HbA1c level and severity of CAD, and outcome of non-diabetic patient with STEMI In our hospital. **Patients and methods:**60 consecutive non diabetic patient with acute ST elevation myocardial infarction were treated with thrombolytic therapy included in the present prospective study. Blood glucose and HbA1c level of all patients were measured within 3 hours of admission. Patient were divided in to 3 groups according to HbA1c level: with cut-off 6.5% as diagnostic criteria of diabetes mellitus according to (American diabetes association) group (1) 6.5% , group (2) 6.5 to 8.5% , group (3) 8.5% and above. In hospital .mortality and morbidities of acute STEMI were compared between groups. **Result :**The mean age was 63±15 year and mean body mass index was 26. 6±6 kg/m² , 24 patients (40%) had history of hypertension , 27 patients (45%) of dyslipidemia, 36 patients (60%) were smoker. We found 45 patients with HbA1c ≤ 6.5%, 5 patients with HbA1c 6.5 -8.5 % , 10 patients with HbA1c ≥ 8.5%. There was strong correlation between admission of HbA1c and admission glucose level (P< 0.001). Infarct size as measured by peak creatinin kinase, was not correlated with HbA1c level. **Conclusion:**HbA1c is an important risk marker in the absence of history of diabetes mellitus in patients with AMI . The optimal management in these patients may contribute in decrease hospital mortality.

Keywords: Glycosylated Hemoglobin (HbA1c); ST elevation myocardial infarction (STEMI); mortalities , Diabetes.

INTRODUCTION:

Patients with diabetes are at 3-4 times increased risk for cardiovascular mortality compared with non-diabetes (Preis PR *et al.*, 2009). In acute coronary syndrome, glucose metabolism is modified and stress hyperglycemia commonly occur secondary to increase catecholamine level (Husband DJ *et al.*, 1983). In addition to the higher rate of acute ST- elevation myocardial infarction (STEMI) in diabetes, hyperglycemia is associated with poor

prognosis in these patients (Wahab N *et al.*, 2002 ;Wiviott S *et al.*,2008;. Li D *et al.*, 2011).

Higher HbA1c level was associated with high cardiovascular disease and death (Selvin E *et al.*,2010). There were some other studies supporting the association between admission serum HbA1c level and increased long-term mortality of non-diabetic patients admitted with STEMI and higher rate CAD in these patients (Timmer J *et al.*, 2011, Pia J *et al.*, 2013). We have evaluated the association of admission level of HbA1c with the

Quick Response Code



Journal homepage:

<http://crosscurrentpublisher.com/ccimb/>

Copyright © 2019 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

DOI: 10.36344/ccijmb.2019.v01i06.005

hospital outcome of non-diabetic patient with STEMI.

PATIENTS AND METHODS:

All patients of both sexes sustaining acute ST elevation myocardial infarction without diabetes were including in the study. Patients with sepsis, hemoglobinopathies or hypothyroidism, tumor , connective tissue diseases, those with sub-acute or chronic MI (longer than 48 hr between first symptom and admission) those with renal failure, hepatic failure , iron deficiency anemia and those with past history of diabetes or used anti diabetic medication were excluded from the study.

Acute myocardial infarction was defined according to the (European Society of Cardiology and American College of Cardiology Criteria).

Increased creatine kinase predominantly in the myocardial band fraction and or increased troponin I (creatin kinase 400 U/L or higher and or cardiac troponin I 2 µg / L or higher) , ischemic symptoms (mainly constrictive chest pain, lasting longer than 30 min) , and or abnormal electrocardiography (ST elevation 1 mm or greater on at least two derivation) . MI was defined as acute if the time elapsed between the first symptom and admission was 48 hr or less .only patients who underwent thrombolytic treatment were included in the study.

All patients were in cardiac care unit , a brief history was obtained from each patient presenting with acute chest pain including presence of risk factors like smoking and hypertension, dyslipidemia and previous history of ischemic heart disease . Clinical examination was done emphasis on signs of cardiac failure , 12 leads electrocardiography (ECG) was done at cardiac care unit and blood sample were sent to laboratory, blood glucose and HbA1c level of all patients were measured within 3 hr of admission regardless of whether they had been fasting or not and for cardiac enzyme. The fasting lipid profile was determined on the morning following admission and

included total cholesterol , high density lipoprotein and triglyceride.

All patients were considered for thrombolytic therapy (Injection streptokinase 1.5 million units over one hour) in the absence of all contraindication the management was according to standard treatment protocol. All patients underwent continues ECG monitoring for at least 48 hour on admission to cardiac care unit and daily during hospital stay.

Patients were divided into three groups according to the level of HbA1c with cut-off 6.5% as diagnostic criteria of diabetes mellitus according to (American Diabetes Association 2010) for diagnosis and classification of diabetes mellitus. Patient with HbA1c level of 4.5% to 6.4 % group (1), patients with HbA1c level 6.5% to 8.5% group (2) and patients with HbA1c level higher than 8.5 % group 3).

None of these patients received glucose , Insulin or potassium infusion therapy during admission. All subjects were hospitalized one week after acute myocardial infarction and hospital records were reviewed at this time.

Selective coronary angiography was performed after 1 month .Coronary angiogram were analyzed by two experienced observers who were blinded to the identities and clinical information of the patients .Vessel scores were ranged from zero to three, according to the number of diseased major pericardial vessel with significant stenosis (greater than 50% stenosis of the lumen diameter).

Statistical analysis: Was performed by using SPSS software (Version 12) difference among groups was analyzed by (t-test) and P value 0.05 was considerable significant.

RESULT:

Table 1: Total 60 patients with STEMT were studied . Patients were divided on the bases of admission HbA1c group (1) ≤ 6.5 %; group (2) 6.5-8.5 %; group 3 ≥ 8.5%.

Table 1: Clinical and biological characteristics of the study subjects. According to admission HbA1c level

	Level of Glycated Hemoglobin				P Value
	All n=60	Group1 <6.5% n=45	Group2 6.5-8.5% N=5	Group3 >8.5 N=10	
Age(year)	63±15	61±15	60±17	70±10	0.02
Sex(M/F)n	48/12	40/5	3/2	7/3	0.4
Current or former smoker(%)	36(60)	29(65)	2(40)	6(60)	
BMI(kg/m ²)	26.6±6	26.1±5	26.7±4.2	29±4.9	0.05
Admission SBP(mmHg)	132±25	129±25	136±22	143±25	0.05
Admission DBP(mmHg)	72±18	72±15	71±14	76±23	0.05
Admission plasma glucose(mmol/L)	8.2±3.7	7.7±2.9	8.2±2.2	11.2±6.5	<0.0001
Total cholesterol(mmol/L)	6±1.2	6.1±1.3	6.3±0.9	5.5±1.1	0.01
HDL cholesterol	1±0.4	1.3±0.4	1.2±0.1	1.2±0.3	0.27

(mmol/L)					
Triglyceride (mmol/L)	1.53±0.89	1.47±0.86	1.88±0.89	1.56±0.99	0.36
Peak CK in first 24 hour(U/L)	903 (210-3256)	1979 (580-3227)	1500 (647-3000)	1486 (504-3126)	NS

Peak CK in first 24 hour (U/L)

Data are mean ± SD, BMI, body mass index ie body weight (kg) / height²(m²). SBP/ DBP, systolic / diastolic blood pressure ; CK. Creatinin kinase.

The clinical and biological characteristic according to HbA1c are summarized in (table 1). The mean age was 63±15 year and mean body mass index was 26. 6±6 kg/m², 24 (40%) had history of hypertension , 27 (45%) of dyslipidemia, 36 (60%) were smoker. We found 45 with HbA1c ≤ 6 .5%; 5 with HbA1c 6.5-8.5%, 10 with HbA1c ≥ 8.5%.

There was strong correlation between admission HbA1c and admission glucose level (P< 0.0001). Infarct size as measured by peak creatinin kinase, was not correlated with HbA1c level.

Table 2: Patients were divided according to admission glucose [group (1), 6.9 mmol/L; group (2), 7 to 8.1 mmol/L; group (3), 8.2 to 9.5 mmol/L; group (4) ≥ 9.6 mmol/ L].

Table 2: Clinical outcome of non-diabetic patients based on quantities of admission plasma glucose.

	Admission Glucose Level				P Value
	IQR1 6.9 mmol/L	IQR2 7-8.1mmol/L	IQR3 8.2-9.5mmol/L	IQR4 ≥9.6mmol/L	
Infarct size	530	903	1367	1912	<0.0001
Peak.CK in the first 24 hr	(210-1150)	(327-2050)	(564-2924)	(827-3256)	

IQR =interquartile range; CK= cratinin kinase. Value are expressed as median(IQR).

There was significant positive correlation between admission glucose and infarct size measured by peak creatinin kinase level (P<0.0001).

Table 3: At the end of fourth week coronary angiography performed in remaining 54 patients, revealed that there was significant correlation between HbA1c level at admission and number of disease vessel(P=0.001).

Table 3:Angiographic data of patients according to HbA1c

Number of diseased vessel N (%)	Level of Glycosylated Hemoglobin			P Value
	Group1 <6.5% N=39	Group2 6.5%-8.5% N=5	Group3 >8.58.5% N=10	
Single vessel	30(76.9%)	3(60%)	1(10%)	0.000
Double vessel	7(17.9%)	1(20%)	4(40%)	0.16
Triple vessel	2(5.1%)	1(20%)	5(50%)	0.001

Table 4: We found that patients who died by day 5 were significantly different from patients with non-lethal acute myocardial infarction, with regard to

admission plasma glucose (16.6 ± 5.4 vs 8.3 ± 3.4 mmol/L , P=0.0001), age (74±10 vs 62 ± 13 year, P=0.002).

Table 4: Clinical characteristics of patients according to the mortality at 5 days after acute myocardial infarction.

	Dead by day 5 N=6	Alive by day 5 N=54	P Value
Age(year)	74±10	62 ± 13	0.002
Sex (M/F)	6/0	42/12	0.33
Peak creatinin kinase (IU/L)	1068 (1120-3256)	825 (210-1860)	0.02
Admission plasma glucose (mmol/L)	16.6 ± 5.4	8.3 ± 3.4	0.0001
HbA1c	6.7 ± 1.8	6.2 ± 0.2	0.15

HbA1c=Glycosylated hemoglobin

There was no significant difference in HbA1c value in the survivor and non-survivor (6.7±1.8 vs 6± 0.2, P=0.15).

DISCUSSION:

The present study confirms previous observation in diabetic subjects suggesting that higher glucose level during AMI are associated with increased mortality (Sewaradsen M, *et al* 1989). In recent study, (Timmer J, *et al.*, 2011) reported that higher admission glucose level in non-diabetic patients treated with reperfusion therapy for ST segment elevation MI were associated with significantly larger enzymatic infarction size and lower left ventricular ejection fraction. This is because a stress response is

accompanied by high level of catecholamine and cortisol and these hormones increase glucogenolysis and lipolysis and reduce insulin sensitivity, resulting in elevated glucose level (Seaquist ER, *et al.*, 2013) There for, patients with elevated glucose level may represent with an increased stress response, due to more sever hemodynamic compromise or more extensive myocardial damage (Gosselink AT., *et al.*, 1998; DeGeare VS, *et al.*, 2001). Elevated cytokine, particularly tumor necrosis factor-Alpha (TNF- α), also increase glucose level. TNF- α is released in AMI and directly decrease myocardial contractility, probably by inducing myocardial apoptosis (Li D, *et al.*, 1999; Li YP *et al.*, 2001). TNF- α also cause impaired endothelial function (Fujita H, *et al.*, 1999). This in turn, may be responsible for the impaired myocardial perfusion. We found positive correlation between peak creatinin kinase and admission plasma glucose concentration in our patients. Conversely, no correlation was found with HbA1c value. Although acute hyperglycemia at admission and during stay has clearly been associated with adverse outcome in patients with acute MI (Capes E, *et al.*, 2000; Norhmmar A, *et al.*, 2002; Timmer J, *et al.*, 2004).

Our study shows admission HbA1c level are not associated with high mortality in non-diabetic STEMI population treated with streptokinase. In our study high HbA1c in non-diabetic patients associated with multivessele involvement of coronary arteries. Similarly (CakMak, *et al.*, 2008) reported a significant correlation between HbA1c level at admission and positive exercise that result after the four week follow up.

Hyperglycemia in STEMI patients was strongly associated with increased mortality within 5 days although there is clear correlation between admission glucose and HbA1c level, they appear to represent related but different phenomena. Patients with elevated glucose level have larger MI area.

Recently a prospective cohort study showed that in non-diabetic general population, as elevated HbA1c level is a risk factor for the development of cardiovascular events independently of fasting glucose (Selvin E, *et al.*, 2009). The international expert committee recommended the use of HbA1c in diagnosis diabetes with a cut-off 6.5 % (Gillet M, *et al.*, 2009).

The advantage of HbA1c over the fast blood glucose are its lower intra-individual variability, assessment in non-fasting state and superior in monitoring blood glucose level (Selvin *et al.*, 2007; American Diabetes Association, 2009). (Preis *et al.*, 2009 Selvin *et al.*, 2010) has suggested that glycosylated hemoglobin is superior to fasting blood glucose in predicting long-term risk of CAD in non-diabetes. Similar result are reported by Park and colleagues among non-diabetic women (Park *et al.*, 1996). In a cohort of European men, khaw and colleagues reported that HbA1c correlates linearly to subsequent cardiovascular morbidity, (Khaw *et al.*, 2001). The American Diabetes Association suggests that individual with HbA1c concentration of 5.7- 6.4% should be informed of their increased risk for diabetes as well as cardiovascular disease (American Diabetes Association 2010).

CONCLUSION:

HbA1c is an important risk marker in the absence of history of diabetes mellitus in patients with AMI. The optimal management in these patients may contribute in decrease hospital mortality. People at high risk for type II diabetes mellitus should receive lifestyle counseling and if needed pharmacological therapy to reduce their risk of developing hyperglycemia and type II diabetes mellitus but especially to prevent or slow the development of CAD.

REFERENCES:

1. American Diabetes Association Diagnosis and classification of diabetes mellitus. (2010). *Diabetes care*;33 *Suppl 1*:S62 - S69. *Doi: 10.2337/dc.10.S062.*
2. Ashraf, H., Boroumand, M. A., Amirzadegan, A., Talesh, S. A., & Davoodi, G. (2013). Hemoglobin A1C in non-diabetic patients: an independent predictor of coronary artery disease and its severity. *Diabetes research and clinical practice*, 102(3), 225-232.
3. Cakmak, M., Cakmak, N., Cetemen, S., Tanriverdi, H., Enc, Y., Teskin, O., & Kilic, I. D. (2008). The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. *Canadian journal of cardiology*, 24(5), 375-378.
4. Capes, S. E., Hunt, D., Malmberg, K., & Gerstein, H. C. (2000). Stress hyperglycaemia and increased risk of death after myocardial infarction in patients

- with and without diabetes: a systematic overview. *The Lancet*, 355(9206), 773-778.
5. DeGare, V. S., Boura, J. A., Grines, L. L., O'Neill, W. W., & Grines, C. L. (2001). Predictive value of the Killip classification in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *The American journal of cardiology*, 87(9), 1035-1038.
 6. American Diabetes Association. (1996). The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*, 45(10), 1289-1298.
 7. Fujita, H., Morita, I., & Murota, S. I. (1999). A Possible Involvement of Ion Transporter in Tumor Necrosis Factor α and Cycloheximide-Induced Apoptosis of Endothelial Cells. *Mediators of inflammation*, 8(4-5), 211-218.
 8. Gerrity, R. G., Natarajan, R., Nadler, J. L., & Kimsey, T. (2001). Diabetes-induced accelerated atherosclerosis in swine. *Diabetes*, 50(7), 1654-1665.
 9. Ghaffari, S., Nadiri, M., Pourafkari, L., Sepehrvand, N., Movasagpoor, A., Rahmatvand, N., ... & Nader, N. D. (2014). The predictive value of total neutrophil count and neutrophil/lymphocyte ratio in predicting in-hospital mortality and complications after STEMI. *Journal of cardiovascular and thoracic research*, 6(1), 35.
 10. Gillett, M. J. (2009). International expert committee report on the role of the A1c assay in the diagnosis of diabetes: diabetes care 2009; 32 (7): 1327-1334. *The Clinical Biochemist Reviews*, 30(4), 197.
 11. Gosselink, A. M., Liem, A. L., Zulstra, F., & Reiffers, S. (1998). Prognostic value of predischarge radionuclide ventriculography at rest and exercise after acute myocardial infarction treated with thrombolytic therapy or primary coronary angioplasty. *Clinical cardiology*, 21(4), 254-260.
 12. Husband, D. J., Alberti, K. G. M. M., & Julian, D. G. (1983). " Stress" hyperglycaemia during acute myocardial infarction: an indicator of pre-existing diabetes?. *The Lancet*, 322(8343), 179-181.
 13. Kassaian, S. E., Goodarzynejad, H., Boroumand, M. A., Salarifar, M., Masoudkabar, F., Mohajeri-Tehrani, M. R., ... & Hakki, E. (2012). Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. *Cardiovascular diabetology*, 11(1), 82.
 14. Khaw, K. T., Wareham, N., Luben, R., Bingham, S., Oakes, S., Welch, A., & Day, N. (2001). Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *Bmj*, 322(7277), 15.
 15. Li, D., Zhao, L., Liu, M., Du, X., Ding, W., Zhang, J., & Mehta, J. L. (1999). Kinetics of tumor necrosis factor α in plasma and the cardioprotective effect of a monoclonal antibody to tumor necrosis factor α in acute myocardial infarction. *American heart journal*, 137(6), 1145-1152.
 16. Li, Y. P., & Reid, M. B. (2001). Effect of tumor necrosis factor- α on skeletal muscle metabolism. *Current opinion in rheumatology*, 13(6), 483-487.
 17. Norhammar, A., Tenerz, Å., Nilsson, G., Hamsten, A., Efendic, S., Rydén, L., & Malmberg, K. (2002). Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *The Lancet*, 359(9324), 2140-2144.
 18. Pai, J. K., Cahill, L. E., Hu, F. B., Rexrode, K. M., Manson, J. E., & Rimm, E. B. (2013). Hemoglobin a1c is associated with increased risk of incident coronary heart disease among apparently healthy, nondiabetic men and women. *Journal of the American Heart Association*, 2(2), e000077.
 19. Park, S., Barrett-Connor, E., Wingard, D. L., Shan, J., & Edelstein, S. (1996). GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes: the Rancho Bernardo Study. *Diabetes care*, 19(5), 450-456.
 20. Preis, S., Hwang, S., Coady, S., Pencina, M.D., Agostino, R., Sr.Savage, P., et al., (2009). Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the -Framingham Heart study, 1950 to 2005. *Circulation* 119: 1728-1735.
 21. Seaquist, E. R., Anderson, J., Childs, B., Cryer, P., Dagogo-Jack, S., Fish, L., ... & Vigersky, R. (2013). Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *The Journal of Clinical Endocrinology & Metabolism*, 98(5), 1845-1859.
 22. Selvin, E., Steffes, M. W., Zhu, H., Matsushita, K., Wagenknecht, L., Pankow, J., ... & Brancati, F. L. (2010). Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *New England Journal of Medicine*, 362(9), 800-811.
 23. Sewdarsen, M., Vythilingum, S., Jialal, I., & Becker, P. J. (1989). Prognostic importance of admission plasma glucose in diabetic and non-diabetic patients with acute myocardial infarction. *QJM: An International Journal of Medicine*, 71(2), 461-466.
 24. joint ESC/ACC Committee. (2000). Myocardial infarction redefined-A consensus document of The Joint ESC/ACC Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*, 36, 959-969.
 25. Timmer, J. R., Hoekstra, M., Nijsten, M. W., van der Horst, I. C., Ottervanger, J. P., Slingerland, R. J., ... & van't Hof, A. W. (2011). Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous

- coronary intervention. *Circulation*, 124(6), 704-711.
26. Wahab, N. N., Cowden, E. A., Pearce, N. J., Gardner, M. J., Merry, H., Cox, J. L., & ICONS investigators. (2002). Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era?. *Journal of the American College of Cardiology*, 40(10), 1748-1754.
27. Wiviott, S., Braunwald, E., Angiolillo, D., Meisel, S., Dalby, A., Verheugt, F., *et al.*, (2008). Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel – *Thrombolysis in myocardial infarction 38. Circulation* 118 : 1626 – 1636.