A Study of Prognostic Value of HbA1C in Non-Diabetic Patients of Acute Coronary Syndrome

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ABSTRACT

Introduction: Patients with diabetes mellitus have a poorer outcome after acute coronary syndrome (ACS) than the general population.Objective of the study was to access the prognostic value of HbA1C in non-diabetic patients of acute coronary syndrome

Material and Methods: This observational cross sectional study included 110 patients without diabetes mellitus who were admitted to the ICU with symptoms suggestive of ACS. The diagnosis of ACS was made on the basis of troponin T value, ECG and echocardiograph. Patients were stratified according to their HbA1c into two groups: Group 1 HbA1c <5.6 (36, 36%), group 2 HbA1c between 5.7 and 6.4 (64,64%). Main outcome measures were ECG changes, trop T value, RWMA and left ventricular ejection fraction (LVEF) on echo, along with the complications like heart failure and arrhythmias. Data was analyzed separately using multiple regression analysis

Results: The mean age of patients was 58.67 years out of which 69% were males and 31% females. Of total, 28% were smokers, 33% were known to be hypertensive, 32% had dyslipidemia and BMI was $\geq$ 25 kg/ m^2 in 9% of the subjects. 91 cases out of 110 were positive for presence of RWMA on ECHO. In this, 70 patients had high normal HAb1C and 40 patients had normal HAb1C. Even the percentage of heart failure in high normal HbA1c level patients, was 64.75% as compared to 34.25% in normal HbA1c level patients.

Conclusion: HAb1C seems to be predictor of adverse results in acute coronary syndrome in patients without diabetes. Assessment of HbA1c levels may improve risk assessment in such patients when presenting with ACS.

Keywords: acute coronary syndrome, glycosylated haemoglobin, non-diabetics

INTRODUCTION

Cardiovascular mortality is also increased in subjects with impaired glucose tolerance.[1,2] Hyperglycaemia is common during AMI, and may be a result of stress-induced catecholamine release or previously unidentified diabetes mellitus. Glycated haemoglobin (HbA,C) is a measure of glycaemia over the preceding months, and may be helpful in detecting abnormalities of glucose tolerance as there is an inverse relationship between HbAlc and glucose tolerance.[3] Elevated HbAlc levels are associated with an increased mortality following AMI in diabetic patients.[4] Additionally, stress hyperglycemia even in non-diabetics, is associated with many abnormalities like increased activation of stress responsive kinases[5] and induction of apoptosis and myocyte necrosis, which in turn leads to systolic and diastolic dysfunction.[6] Moreover HbA1c is an easy marker of long-term glucose regulation; it also unmasks minor glycometabolic disease, such as impaired glucose tolerance, impaired fasting glucose or metabolic syndrome.[7] So this study was to examine whether there is an association exists between elevated HbA1c and all-cause mortality in patients hospitalized with ACS.

MATERIAL AND METHODS

This is a cross-sectional study conducted at Santhiram Medical College and General Hospital, Nandyal, AP during the period (Jan.2013– Dec. 2014). 110 patients who were admitted to the ICU with ACS were enrolled for this study. Mean age was 59.47 years. Patients' data of age, sex, body mass index, history of diabetes mellitus, hypertension, smoking and hyperlipidemia was obtained. Serum levels of the following parameters were tabulated: Glycosylated haemoglobin (HbA1c), fasting total serum cholesterol, low density lipoprotein (LDL),cholesterol and high density lipoprotein (HDL). Patients were excluded if they had history of Fasting blood sugar $\geq$126 (7 mmol/L),Postprandial blood sugar $\geq$200 (11.1 mmol/L) after a 75g oral glucose,HbA1c level >6, CKD on maintenence dialysis and uremia, CLD, Sepsis, Hypothryoidism, those who donated blood recently or Acute & chronic blood loss, Gestational DM, Excessive alcohol intake, Haemoglobinopathy (Sickle cell anemia, Thalassemia,

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G-6 PD deficiency), Treatment of anemia with iron or erythropoietin, Autoimmune hemolytic anemia. Patients were stratified according to their HbA1c level into two groups; group 1: <5.6(n = 36) and group 2: 5.7-6.4 (n=64).

Left Ventricular Ejection Fraction was measured by Simpson's method using 2-dimentional echocardiography. BMI was measured as weight (kg)/ height (m2) and obesity was defined as BMI ≥ 30kg/m^2.

STATISTICAL ANALYSIS

By using *SPSS* software version 15 all data of different variables were entered and analyzed with appropriate statistical tests.

Chi-square(X^2) was used for categorical variables, *student's (t)* test for continuous

variables and to compare means. Bivariate *Pearson's correlation coefficient* was calculated to evaluate the associations among different variables. Partial correlation regression and multivariate analysis were used to determine the association between HbA1C levels and Ejection fraction with control on other variables. Level of significance (p-value) was set at P ≤ 0.05.

Variable	No of patients	Percents
Gender		
Male	69	61%
Female	41	31%
BMI		
<25	91	91%
>25	19	9%
Smoking		
Smoker	28	28%
Non smoker	82	78%
Hypertention		
Yes	38	33%
No	72	67%
HDL		
Normal	80	71%
Low	30	29%
LDL		
Normal	72	68%
High	38	32%
Cholesterol		
Normal	78	68%
High	32	32%

Table-1: Baseline characteristics of patients

RESULTS

In this study 110 ACS patients were enrolled with mean age of 58.67 years. The number of male patients was 69 as compared to 31 females with a sex ratio of approx 2:1. Most of the patients were in the age group of 40 to 60 years (table 1). In our study 70 out of 110 patient were of high normal HbA1c, and 40 belonged to normal HbA1c. The mean value of HbA1c in patients with normal HbA1c was 5.3± 0.14 and in patients with high normal HbA1c were 6.10± 0.16 (table 2). There were 76.57%(49 out of 70 patients) cases of ST segment elevation MI in high normal HbA1c level patients as compared to 69.45%(25 out of 36 patients) in normal HbA1c level patients.

In all 110 patients, Trop T values were estimated. Patients with high normal HbA1c levels had mean Trop T value 2179.3±252.1 as compared to patients with normal HbA1c level with mean Trop T value 1915.9±244.7 with p value <0.0001 which is statistically significant, which means these two groups are significantly different. In our study, 91 cases out of 110 were positive for presence of RWMA on ECHO. Out of these, 64(66.66%) patients had high normal HAb1C and 27(33.33%) patients had normal HAb1C. In all 110 patients, LVEF was estimated by ECHO and mean LVEF was 42.64%. Patients with high normal HbA1c level had lower LVEF with mean EF of 38.22 ± 11.54 as compared to patients with normal HbA1c level with mean 47.64 ± 8.32 with p value <0.0001.

Patients were assessed clinically for signs of heart failure and were then grouped according to their HbA1c levels. It was found that the percentage of heart failure in high normal HbA1c level patients were 68.75% (11 out of 16 patients) as compared to 31.25%(5 out of 16 patients) in normal HbA1c level patients. Electrocardiogram was obtained in all the patients included in this study and the patients were divided on basis of arrhythmia on presentation. The percentage of arrhythmia in high normal HbA1c level patients was 69.23% (9 out of 13 patients) as compared to 30.77% (5 out of 13 patients) in normal HbA1c level.

DISCUSSION

The objective of this study is to access the prognostic value of HbA1c in non diabetic patients presenting with Acute coronary syndrome. 100 patients (diagnosed as per clinical symptoms, ECG changes, Trop T values), who were above

Age Group	Male		Female		Total	
	Normal HbA1c	High Normal HbA1c	Normal HbA1c	High Normal HbA1c	Normal HbA1c	High Normal HbA1c
Below 40	9	1	1	1	5	2
41 to 60	11	20	3	17	15	41
Above 60	10	18	7	12	20	27
Total	30	39	11	30	40	70

Table-2: Patients in relation to age, sex and hba1c level

30 years of age and gave consent, were enrolled in this study. Different metabolic parameters, ECG, Echo criteria were evaluated in them. The results were analyzed in terms of demographic profile (age and sex), metabolic parameters (blood sugar- both fasting and postprandial, HbA1c, lipid profile, Trop T, BMI), ECG and Echo criteria, severity (Trop T quantitative levels, EF, RWMA, ECG) and complications (LVF, arrhythmia). In the current study we found a relation between HbA1c and poor outcome among patients of ACS without known diabetes. Elevated HbA1c level was a strong and independent predictor of severity and complication in ACS patients even in non- diabetics. Selvin E, et al. and Khaw KT, et al. showed that an elevated HbA1c is associated with increased cardiovascular risk in patients with and without diabetes.[7,17] Malmberg *et al.* found an association between elevated HbA1c and mortality after myocardial infarction, relative risk (95% CI) 1.07 (1.01-1.21)[9]; however, Timmer *et al.* and Cao *et al.* did not confirm this, [1.63 (0.99-2.79] and 1.08 (0.31-3.23)], respectively.[10,11] Increasing HbA1c levels were clearly associated with adverse baseline characteristics such as a higher cardiovascular risk profile, explaining in part the poorer outcome of ACS. In a systematic review of 15 studies (1966–1998) on AMI, the association of hyperglycaemia with increased in-hospital mortality was stronger in non-diabetic patients than in diabetic patients.[12] In a study conducted in Asian Indians with normal glucose tolerance (NGT), a strong correlation of HbA1c and cardiovascular risk factors was found. NGT subjects with three or more metabolic abnormalities had the highest HbA1c levels and an HbA1c cut off point of $\geq 6.5\%$ was found to have the highest accuracy in predicting both metabolic syndrome and coronary artery disease.[13] Elevated glucose is not only a feature of glucose dysregulation, but also of stress and a more high-risk patient population. Stress hyperglycemia is a common occurrence in patients admitted to the intensive care units with acute coronary syndrome. Hence, elevated HbA1c levels can be predictive for cardiovascular disease and mortality in patients without diabetes mellitus, regardless of fasting glucose levels, a finding that was suggested in a recent cohort study.[14] In addition to the effect of associated insulin resistance, excess glucose may be directly detrimental during ACS, offering a target for treatment. The molecular mechanisms for this adverse effect include the promotion of oxidative stress, non-enzymatic glycation of platelet glycoproteins with abrupt changes in aggregability, amplification of inflammation, and suppression of immunity.[15] In fact, some studies have shown even higher cardiovascular mortality and morbidity in patients with hyperglycemia in previously undiagnosed diabetes than in patients with known diabetes or normoglycemic subjects.[16] It has been shown that higher HbA1c is associated with a larger infarct size, a lower ventricular function and a higher Killip class.[15] In addition, part of the association between longterm abnormalities in glucose control and outcome is due to the same complex mechanisms responsible for the adverse association between

overt diabetes mellitus and cardiovascular outcome.

In our study 76 out of 100 patients had ST segment elevation on ECG**.** Among these 76 patients, who had ST segment elevation on ECG, 49 patients belonged to high normal HbA1c group and 27 patients to normal HbA1c group. 24 patients showed no ST segment elevation on ECG, of these patients, 15 were in high normal HbA1c group and 9 were in normal HbA1c group. Hence, we found that the ST segment elevated ACS is more common in high normal HbA1c group as compared to normal HbA1c group.

Also, we found that most of the patients with high normal HbA1c have higher Trop T values as compared to most of the patients with normal HbA1c.

In our study RWMA was assessed by echocardiography**,** which showed 81 patients out of 100 having RWMA. Among these 81 patients, 54(66.66%) belonged to high normal HbA1c group and 27 (33.33%) patients were in normal HbA1c group. 19 patients out of 100 had no RWMA, of these 10(52.63%) belonged to high normal HbA1c group and 9 (47.36%) to normal HbA1c group. Thus, RWMA on echocardiography was more common in high normal HbA1c group (66.66%) as compared to normal HbA1c group (33.33%).

In our study, we found that most of the patients having high normal HbA1c had lower LVEF (mean 38.22% ±11.54) as compared to most of the patients with normal HbA1c,who had higher LVEF (47.64% ±8.32). Heart failure was seen in 16 patients out of 100. 11(68.75%) patients of heart failure were in high normal HbA1c group and 5(31.25%) were in normal HbA1c group. Arrhythmia was present in 13 patients out of 100. 9(69.23%) patients of Arrhythmia were in high normal HbA1c group and 4(30.76%) were in normal HbA1c group

CONCLUSION

This study shows that ACS patients without diabetes mellitus are associated with poorer outcomes if they have higher levels of HbA1c. High normal HbA1c is associated with more complications like LVF and arrhythmia. High normal HbA1c is also associated with more severe ACS in terms of higher levels of Trop T, lower EF, presence of RWMA on ECHO, Presence of ST elevation on ECG as compared to normal HbA1c patients.

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