Impact of HbA1c on Outcomes of Acute Coronary Syndrome in Non-Diabetic Patients

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Abstract: *Background*: Elevated glucose levels have been previously shown to be associated with adverse outcomes in patients of acute coronary syndrome. However, admission glucose levels are affected by various factors like meals, circadian cycle and also the stress response. HbA1c is a better marker of long- term glucose status. The value of HbA1c as a predictor of prognosis in acute coronary syndrome has not been extensively studied.

Objective: To study the relationship between admission HbA1c levels and short-term outcome in non-diabetic patients admitted with acute coronary syndrome.

Material and Methods: This open-label, hospital based, cohort study was conducted on 200 patients without previously known diabetes admitted with acute coronary syndrome. A detailed history and clinical examination were carried out. Admission plasma glucose, fasting glucose and HbA1c levels were recorded. Those presenting with fasting plasma glucose of >126 mg% or HbA1c >6.5% were labeled as "Undiagnosed Diabetic Patients". Outcome was measured mainly by assessing the left ventricular systolic function. Data were analysed using chi square test, student t-test, ANOVA and partial correlation regression, wherever applicable.

Results: Mean age of patients was 56.38 years. Average BMI was 25.1±3.5 kg/m2. Mean HbA1c was 6.3±1.5%. 79 (39.5%) patients had HbA1c between 6 and 6.5. There was a linear correlation between ejection fraction and HbA1c (p value =0.019).

Conclusion: HbA1c is a strong predictor of left ventricular dysfunction in non-diabetic patients presenting with acute coronary syndrome, therefore, measurement of HbA1c levels may improve risk assessment in patients presenting with acute coronary syndrome.

Keywords: HbA1c, Acute Coronary Syndrome.

INTRODUCTION

Hyperglycemia in acute coronary syndrome is associated with a poor prognosis [1]. Although stress hyperglycemia is common in all patients of acute coronary syndrome, poor prognosis has been associated with those patients who tend to have persistent hyperglycemia [2]. Previous studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients of type 2 diabetes mellitus, as it is a measure of mean glucose level during the previous 2-3 months [3].

The Framingham heart study has shown that the cardiovascular mortality is twice in diabetic men and four times in diabetic women as compared to their non-diabetic counterparts [4]. HbA1c levels of >7% are associated with a significant increase in the risk of cardiac events and deaths [5]. This has further been shown that the higher HbA1c levels are associated with increased cardiovascular mortality even before the diagnosis of diabetes is made [6].

Whether HbA1c levels have the same prognostic significance as glucose levels in acute coronary syndrome is unknown. The value of admission HbA1c level in patients with acute coronary syndrome has been studied in a limited number of studies [7]. Recent evidence has shown that chronic glucose dysregulation, assessed by HbA1c levels, is also of prognostic value with regard to future coronary artery disease [8].

Although admission glucose has good prognostic value on outcome in ACS, it may be affected by meals, the circadian cycle, and also the stress response. A few recent studies have evaluated the role of HbA1c in diabetic patients presenting with acute coronary syndrome, a host of other concomitant factors may act as confounding factors, in diabetic patients [9]. Endothelial dysfunction has been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease 10]. Diabetes may predispose to coronary thrombosis through increased primary and secondary platelet aggregation, and increased platelet activation [11]. In addition to platelet activation, diabetes is associated with an increase in plasma fibrinogen, which is a cardiovascular risk factor.

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The impact of HbA1c in non diabetic patients presenting with acute coronary syndrome has not been extensively studied and there are very few studies cited in literature which address this fact [12].We investigated the independent role of HbA1c on outcomes in patients of acute coronary syndrome without previously known diabetes.

MATERIAL AND METHODS

The present study is an open label, hospital based cohort study, conducted in a tertiary care hospital in India. The study was conducted over a period of one year. A total of two hundred patients were studied, which included non-diabetic patients presenting with Acute Coronary Syndrome, i.e. Unstable angina (UA); ST-Segment Elevation Myocardial Infarction (STEMI) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI).

The exclusion criteria were:

1.   Previously known diabetic patients.

2.   Patients with atypical chest pain.

3.   Patients with chronic stable angina, not presenting with an acute event.

4.   Patients with an alternative cause of chest pain.

A detailed history and clinical examination were carried out. Demographic characteristics including age, sex, socioeconomic status and lifestyle were taken into account. The medical history included the presence or absence of chest pain. If chest pain was present, the nature of pain, its duration and radiation were noted. Any anginal equivalents like sweating, palpitations or breathlessness were also asked for. A thorough clinical examination was carried out, including pulse rate and blood pressure recording, presence of additional heart sounds, rales, evidence of heart failure etc.

Laboratory Assessment

Plasma glucose was measured using Glucocard 01 mini glucometer based on the Glucose Oxidase method (*Aspergillus niger* sourced). The glucose values of all patients were recorded at the time of admission; it was followed by a fasting value recorded next morning. The HbA1c was measured using kits provided by Bio-Rad Laboratories Inc, Hercules, California, USA, based on the ion-exchange high performance liquid chromatography (HPLC). Cardiac

Troponin I was measured quantitatively in all patients admitted with a diagnosis of acute coronary syndrome in the coronary care unit, using AxSYM Troponin I *ADV* kit provided by Abbott laboratories. 2-D Echocardiography was done in all patients after one week of admission to look for any echocardiographic evidence of myocardial dysfunction, Regional Wall Motion Abnormality (RWMA) and to measure the ejection fraction which was a major deciding factor for prognosis in the subjects.

Statistical Analysis

SPSS version 21 was used for all statistical analysis. All data are described as rates and frequencies or means with standard deviations, as appropriate. *Chi square test* was used for categorical variables and *student's t test* was used for continuous variables. One way ANOVA with post hoc correction using *Tukey's test* was used to compare two or more groups respectively. Bivariate *Pearson's Correlation coefficient* was calculated to evaluate the associations among different variables. *Partial Correlation Regression* was used to determine the association between HbA1c and Ejection Fraction with controlling of other variables.

RESULTS

Table **1** shows the comparison of demographic, clinical and laboratory parameters of patients according to HbA1c levels. Of the total 200 patients presenting with acute coronary syndrome, 85 (42.5%) presented with STEMI, 53 (26.5%) presented with NSTEMI and 62 (31%) presented with unstable angina. The mean age was 56.38±13.3 years. The average BMI was 25.1±3.5 kg/m^2. 78 patients (39%) were found to be hypertensives. 94 (47%) patients were smokers and family history of coronary artery disease was present in 72 (36%) patients. 11 patients (5.5%) had a previous history of stroke. 79 (39.5%) patients had HbA1c between 6 and 6.5. On applying partial correlation regression, association between HbA1c levels and ejection fraction was found to be significant with a p-value of 0.019 (Table **2**). A linear decrease in ejection fraction was found with raised level of HbA1c (Figure **1**).

DISCUSSION

We have found a relation between HbA1c levels and poor outcomes in patients of acute coronary syndrome. In the present study, increasing HbA1c

Table 1:   Comparison of Demographic, Clinical & Laboratory Data According to HbA1c Levels

Variable		HbA1c levels						P-Value
		5.5-6.4		4.5-5.4		<4.5		
Patients	Number/%	165	82.5	19	9.5	16	8	0.022
Male	Number/%	118	71.5	13	68.4	14	87.5	0.041
Age yrs	Mean/SD	53	13.5	59.7	13	55.4	12.8	0.759
Prior CAD	Number/%	45	27.3	4	21.1	8	50	0.003
BMI	Mean/SD	27.9	3.4	26.1	4.3	27.4	3.6	0.006
Hypertension	Number/%	60	36.4	9	47.4	9	56.3	0.001
Smoking	Number/%	77	46.7	12	63.2	5	31.3	0.071
Family History	Number/%	58	35.2	8	42.1	6	37.6	0.001
Previous stroke	Number/%	8	4.8	1	5.3	2	12.5	0.074
Aspirin	Number/%	35	21.2	2	10.5	8	50	0.144
Clopidrogel	Number/%	13	7.9	1	5.3	4	25	0.071
Beta-blocker	Number/%	36	21.8	3	15.8	4	25	0.460
Statin	Number/%	34	20.6	3	15.8	8	50	0.076
Nitrate	Number/%	19	11.5	1	5.3	2	12.5	0.282
Diuretic	Number/%	17	10.3	2	10.5	5	31.3	0.110
CEI/ARB	Number/%	29	17.6	3	15.8	4	25	0.688
CCB	Number/%	14	8.5	2	10.5	1	6.3	0.978
Hemoglobin g/dl	Mean/SD	12.0	1.9	11	1.9	12.6	1.9	0.374
S.Creatinine mg/dl	Mean/SD	1.2	0.8	1.1	0.5	1.6	0.8	<0.001
Troponin I, ng/ml	Mean/SD	9.8	1.2	8.8	1.7	6.1	3.1	0.001
T.Cholesterol, mg/dl	Mean/SD	184.3	40.2	164.6	69.4	165	50	0.005
LDL –C mg/dl	Mean/SD	105.4	27.7	93.6	51.8	99.9	34	0.03
HDL-C mg/dl	Mean/SD	40.7	9.7	45.4	14.1	41.2	10	0.749
Triglycerides mg/dl	Mean/SD	145.6	54.5	127.4	32.9	147.7	44.6	0.128
Admission Glucose, mg/dl	Mean/SD	155.6	59	131.8	50.1	271	89.2	<0.001
Fasting Glucose	Mean/SD	113.9	33.6	102.1	27.9	98.4	51.7	<0.001
Ejection Fraction, %	Mean/SD	39.3	13.8	42.4	10.1	48.1.4	12.1	0.004
Length of stay (days)	Mean/SD	5.1	1.3	4.8	0.7	41	1.6	0.290
Mortality	Number/%	7	1.8	4	21	3	43.8	0.01

CAD: Coronary Artery Disease; BMI: Basal Metabolic Index; CEI: Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker; LDL: Low Density Lipoproteins; HDL High Density Lipoproteins.

Table 2:   Model Summary and Parameter Estimates between HbA1c and Ejection Fraction

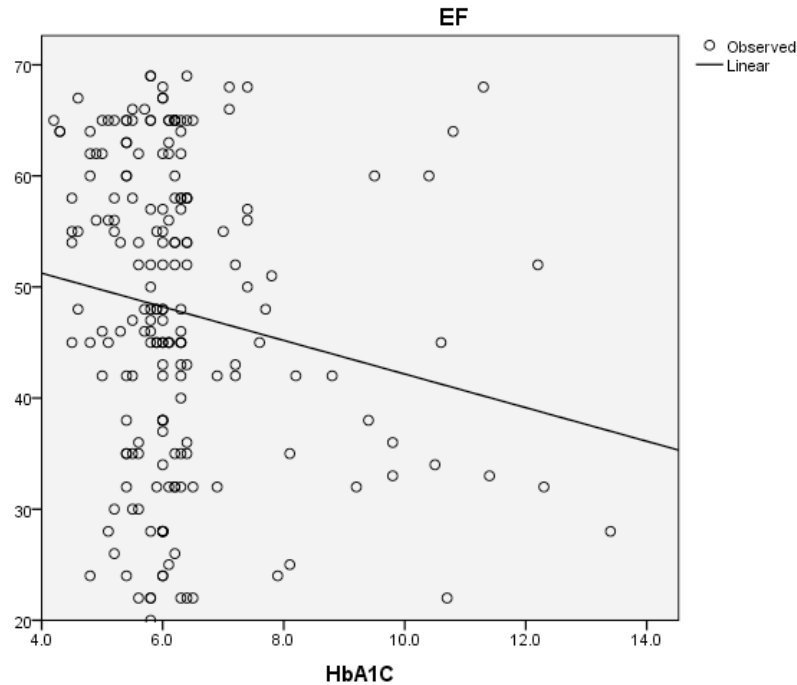| Equation	Model Summary					Parameter Estimates	
	R Square	F	df1	df2	Sig.	Constant	b1
Linear	.027	5.563	1	198	.019	57.291	-1.513

Figure 1: Correlation between HbA1c and ejection fraction in acute coronary syndrome.

levels were clearly associated with adverse baseline characteristics such as a higher cardiovascular risk profile, explaining part of the poor outcome of ACS.

In the current study, the mean age of patients was 56.38±13.3 years. Youngest patients were in the group with HbA1c 5.5-6.4%. This is commensurate with a previous study by Chi Yuen Chan *et al.* [13]. The reason behind younger patients presenting with higher HbA1c levels could be that elevated HbA1c is associated with increased risk of macrovascular damage and accelerated atherosclerosis. Hence theses patients present earlier compared to those with lower HbA1c levels.

BMI was highest in the current study among patients presenting with HbA1c in the range of 5.5-6.4%. This was in concert with a previous study by Manal Khudhur Abdul Razzaq *et al.* [12]. This depicts the increase in incidence of metabolic syndrome as HbA1c rises. HbA1c has been shown to be an independent predictor of metabolic syndrome, even in patients with normal glucose tolerance [14]. This outlines the fact that HbA1c is associated with increased cardiovascular risk, independent of glucose tolerance in predisposed individuals. A significant correlation was found between BMI and HbA1c in the present study with a p-value of 0.006.

Mean HbA1c in the current study was 6.3±1.5%. Majority of non-diabetic patients in the current study

had HbA1c levels between 6-6.5%. 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 ≥ 6.5% was found to have the highest accuracy in predicting both metabolic syndrome and coronary artery disease [15]. However, a confounding factor was the use of certain drugs which are known to affect HbA1c levels. 43 of our patients were on beta blockers. Beta blockers are known to increase HbA1c levels [16]. Also, 24 patients in the current study were on thiazide diuretics. Thiazides are also known to increase HbA1c levels[17]. These may be acting as confounding factors in our study.

Mean troponin levels were highest among patients presenting with HbA1c 5.5-6.4% (9.8±3.1 ng/ml). Cardiac troponin depicts the infarct size. A statistically significant correlation was found between HbA1c and troponin levels with a p-value of 0.001. This has already been shown in previous studies that cardiac troponin correlates with infarct size [18]. Higher the value of troponin, larger is the infarct size.

Elevated HbA1c levels on admission have been found to be associated with reduced ejection fraction and ejection fraction is known to represent the outcome and prognosis in acute coronary syndrome [19]. We

applied partial correlation regression to evaluate the relationship between HbA1c levels and ejection fraction. The R factor came out to be 0.027, with a p value of 0.019, suggesting a statistically significant association between elevated HbA1c and reduced ejection fraction in patients of acute coronary syndrome. Since ejection fraction correlates with outcome and prognosis in acute coronary syndrome, our results directly outline the significance of elevated HbA1c in poor outcomes in patients of acute coronary syndrome.

CONCLUSION

The current study has shown that higher HbA1c levels are associated with adverse outcomes in patients of acute coronary syndrome, irrespective of the previously known diabetic status of the patient. Partial correlation regression has shown an association between HbA1c levels and ejection fraction in acute coronary syndrome. Thus the present study has established the fact that HbA1c on admission is a powerful predictor of left ventricular systolic functions in acute coronary syndrome and therefore, measurement of HbA1c levels may improve risk assessment in patients presenting with acute coronary syndrome.

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