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Research Article

HBA1c Levels In Non-Diabetic Patients with ST Elevated Myocardial Infarction & its Correlation with Short Term Mortality

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Abstract:

Background: Elevated HBA1C level is predictive for cardiovascular disease and mortality in diabetic & also in non-diabetic patients. Aim of our study was to evaluate correlation between HBA1c on admission and short term mortality in non-diabetic patients with ST elevated myocardial infarction.

Methods: 266 non-diabetic patients presenting with STEMI (within 48 hours) were included in our study. Data regarding patient characteristics were collected over 7 months. All-cause mortality data collected prospectively up to 6 months.

Results: Mean HBA1C was 5.69±0.65 for the study population. HBA1C quartiles (<5, 5.1-5.5, 5.6-6, 6.1-6.4) has shown increased 6 months mortality (3%, 4.8%, 1.7%, 15.1% respectively P=0.004) with increased values. Multivariate regression analysis has shown HBA1C>6 as an independent predictor of 6 month mortality.

Conclusion: A significant correlation exists between HBA1C on admission in non-diabetic patients with STEMI and 6 month all-cause mortality.

Keywords: stemi, hba1c, non-diabetic, all-cause mortality

Introduction:

Acute glycometabolic derangement in non-diabetic patients with myocardial infarction is a powerful predictor of prognosis. Elevated HBA1C levels are predictive for cardiovascular disease and mortality in patients without DM indicating that long-term glycometabolic derangement in the sub diabetic range also poses a risk for cardiovascular disease [1] A recent report by Timmer JR et al has found that increase in HbA1c levels was predictive of cardiovascular disease and mortality in patients without diabetes mellitus [2].Increasing HbA1c levels were clearly associated with adverse baseline characteristics such as a higher cardiovascular risk profile, explaining part of the increase in long-term mortality. Among non-diabetic adults attended in a second visit of the Atherosclerosis Risk In Communities (ARIC) study, higher HbA1c level was associated with higher cardiovascular disease and death [Selvin et al. 2010]. In the Rancho Bernardo cohort [3] of 1239 older non-diabetic adults, baseline HbA1c but not fasting or post-challenge glucose predicted cardiovascular mortality in women but not in men. In addition, it is conceivable that part of the association between long-term 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. Indeed, it has been well established that the excess risk for developing coronary artery disease is not limited to patients with diabetes

mellitus but also is present in impaired fasting glucose, impaired glucose tolerance, and other states of insulin resistance. Pai et al. [4], conducted parallel nested case-control studies in 2 cohorts of US health professionals, in non-diabetic women (Nurses' Health Study) and men (Health Professionals Follow-up Study) and found that compared with HbA1c of 5.0% to <5.5%, those with an HbA1c of 6.0% to <6.5%, the pooled relative risk of CAD was 1.29 (95% CI 1.11–1.50) for every 0.5%-increment increase in HbA1c levels and 1.67 (95% CI 1.23–2.25) for every 1%- increment increase, with the risk plateauing around 5.0%. Furthermore, participants with HbA1c levels between 6.0% and <6.5% and CRP levels >3.0 mg/l had a 2.5-fold higher risk of CAD compared with participants in the lowest categories of both biomarkers. A recent meta-analysis also examined the association between HbA1c and risk of CAD in people without diabetes. The European guidelines on diabetes mellitus, prediabetes, and cardiovascular disease recommend that people at high risk for type 2 diabetes mellitus should receive lifestyle counselling and, if needed, pharmacological therapy to reduce their risk of developing overt hyperglycaemia and type 2 diabetes mellitus especially to prevent or slow the development of cardiovascular disease. This approach could also be encouraged in our patient population, and it may alter prognosis. However, it is known that the overall increase in cardiovascular risk in patients with diabetes mellitus or milder abnormalities in glucose levels is not explained by abnormalities in

glucose or HbA1c alone, which is an important consideration in designing prevention efforts.

Hyperglycaemia is common during AMI, and may be a result of stress-induced catecholamine release or previously unidentified diabetes mellitus. Glycated haemoglobin (HbA1C) 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. Acute glycometabolic derangement in non-diabetic patients with myocardial infarction has already been proven to be a powerful predictor of prognosis by Goyel A et al [5]. Until now, data on the predictive value of HbA1c levels, reflecting long-term glycometabolic control, in non-diabetic patients with myocardial infarction are limited as observed by Hudjaj et al in his article [6]. In this background, we have conducted our study on HbA1C levels in blood on admission in non-diabetic patients presented with STEMI and its correlation with short term all-cause mortality.

Objective:

To evaluate correlation between HBA1c levels in blood on admission and short term mortality in non-diabetic patients with ST elevated myocardial infarction.

Materials and Methods:

Our study was a single centre (SJIC&R) observational (cross sectional) study with short term follow up (6 months) Period of data collection was from August 2016 to February 2017(7 months). A proforma was predesigned for data collection. Written informed consent was taken from the study participants. Study consisted of history, study of angiographic report and relevant biochemical investigations. It consisted of patient details like hospital number, name, age, gender, history of diabetes, smoking, dyslipidemia, hypertension and other co-morbidities. Definitions used were as follows:

STEMI (O'Gara PT et al 2013 ACCF/AHA guidelines)

DIABETES MELLITUS (as per ADA criteria)

HYPERTENSION (as per ESH/ESC 2013 criteria)

HYPERLIPIDEMIA (as per NCEP ATP III criteria)

Details of the angiography were obtained and weighed using SYNTAX score. The SYNTAX scores were calculated with the help of professional website tool: http://www.syntaxscore.com/. Serum concentration of HbA1c was determined by immunoturbidometric method. Mortality data (All-cause mortality) was collected prospectively. It included in hospital mortality & mortality after 6 months.

- INCLUSION CRITERIA:

  Non-diabetic patients presented with ST elevated myocardial infarction within 48 hours of symptom onset were included in the study.

- EXCLUSION CRITERIA:

  o MI patients presented after 48 hrs of symptom onset.
  o NSTEMI & Unstable angina patients.
  o H/O prior revascularisation (PCI or CABG)
  o Anaemia(Hb<10 g/dl), hemoglobinopathies
  o Recent H/O-blood transfusion.
  o Splenectomy
  o Drugs-ART, dapsone, ribavirine

  o Treatment with EPO, Iron, Vit B 12

Statistical Analysis:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Assumptions:

1. Dependent variables should be normally distributed,

2. Samples drawn from the population should be random, Cases of the samples should be independent Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher exact test used when cell samples are very small. Multivariate logistic regression was used to show HbA1c level as independent predictor of severity of CAD & all-cause mortality at 6 months. Significant figures :+ Suggestive significance (P value: 0.05<P<0.10) .* Moderately significant (P value:0.01<P £ 0.05)   ** Strongly significant (P value : P£0.01) Statistical software: The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results:

Baseline characteristics are summarised in table 1.Mean age of the study population was 52.71±11.4 years. Most of the patients were male. Hypertension (22.9%) and smoking (26.3%) were most common cardiovascular risk factors. Most of patients presented in KILLIP class I (92.4%). Maximum patients (65.8%) had ejection fraction in 40-50% range. Few (16.5%) patients had ejection fraction<40%. Angiographically most of the patients had significant LAD disease (57.9%) and RCA disease (38.3%), very few patients had LMCA disease (0.8%). 16.5% patients had multi-vessel disease .Most of them (79.7%) had low <11 SYNTAX score. Only 0.4% patients had >22 SYNTAX score, rest patients (19.9%)had 11-22 SYNTAX score. 43.6% patients were treated with thrombolysis, 13.2% patients underwent primary PTCA. Eventually most of the patients (80.4%) underwent PTCA (including primary & pharmacoinvasive). Very few patients underwent CABG. 1.1% patients had in hospital mortality. 5.3% patients had mortality after 6 months.

HBA1C mean was5.69±0.65. In subgroup analysis of HBA1C quartiles of patients, (figure 1) 33 patients(12.4%) have HBA1C<5(subgroup 1), 63 patients(23.6%) have HBA1C 5 to 5.5 (subgroup 2), 117 patients(43.9%) have HBA1C 5.6 to 6(subgroup 3), 53 patients(19.9%) have HBA1C 6.1 to 6.4(subgroup 4). Mean SYNTAX scores in these 4 subgroups are significantly different(2.65, 5.53, 7.15, 13.42 respectively)(p<0.001) & it is increasing with increasing HBA1C values.(table 2). 6 month all-cause mortality also are significantly different in these 4 subgroups (3%, 4.8%, 1.7%, 15.1% respectively)(p=0.004) & increasing with increasing HBA1C values (table 2)(figure 1). Multivariate analysis has shown that HBA1C>6.0 is an independent predictor of mortality as a risk factor(p<0.001) in our study (table 3).

Age (mean)			52.71±11.4 years
Sex	Male		238 (89.5%)
	Female		28 (10.5%)
Risk factors	Smoking		70 (26.3%)
	Dyslipidemia		26 (9.8%)
	Hypertension		61 (22.9%)
Clinical presentation		KILLIP I	247 (92.8%)
		KILLIP II	13 (4.9%)
		KILLIP III	1 (0.4%)
		KILLIP IV	5 (1.9%)
Ejection fraction(%)		<40	44 (16.5%)
		40-50	175 (65.8%)
		>50	47 (17.7%)
HBA1C (mean)			5.69±0.65
HBA1C quartiles		<5	33 (12.4%)
		5-5.5	63 (23.6%)
		5.6-6	117 (43.9%)
		6.1-6.4	53 (19.9%)
Coronary artery involvement		LMCA	2 (0.8%)
		LAD	154 (57.9%)
		LCX	49 (18.4%)
		RCA	102 (38.3%)
Multivessel disease			44 (16.5%)
Syntax score		<11	212 (79.7%)
		12-22	53 (19.9%)
		>22	1 (0.4%)
Treatment		Thrombolysis	116 (43.6%)
		Primary PTCA	35 (13.2%)
		PTCA (Total)	214 (80.4%)
		CABG	2 (0.8%)
Mortality(all-cause)		In hospital	3 (1.1%)
		6 months	14 (5.3%)

Table 1: Baseline characteristics (N=266)

VARIABLES	<5 (n=33) (Subgr 1)	5-5.5 (n=63) (subgr 2)	5.6-6 (n=117) (subgr 3)	6.1-6.4 (n=53) (subgr 4)	P VALUE
Syntax score(mean)	2.65±2.72	5.53±2.11	7.15±2.21	13.42±3.36	<0.001**
6 month mortality	1(3%)	3(4.8%)	2(1.7%)	8(15.1%)	0.004**

Table 2: HBA1C quartiles subgroup analysis in non-diabetics (correlation with 6 month all-cause mortality)

VARIABLES	Logit co-efficient	SE	Wald	P value	Adj OR	95% CI LOWER	95% CI UPPER
Age >60 years	0.37	0.41	0.80	0.372	1.45	0.64	3.26
Male	-0.43	0.50	0.73	0.392	0.65	0.25	1.73
Hypertension	-0.61	0.47	1.68	0.195	0.55	0.22	1.36
Dyslipidemia	0.11	0.57	0.04	0.851	1.11	0.37	3.38
Smoking	-0.29	0.53	0.30	0.586	0.75	0.26	2.13
HbA1c>6.0	**1.98**	**0.48**	**17.14**	**<0.001****	**7.21**	**2.83**	**18.36**

Table 3: Multivariate Logistic regression analysis to assess the risk factors of 6 month all-cause mortality
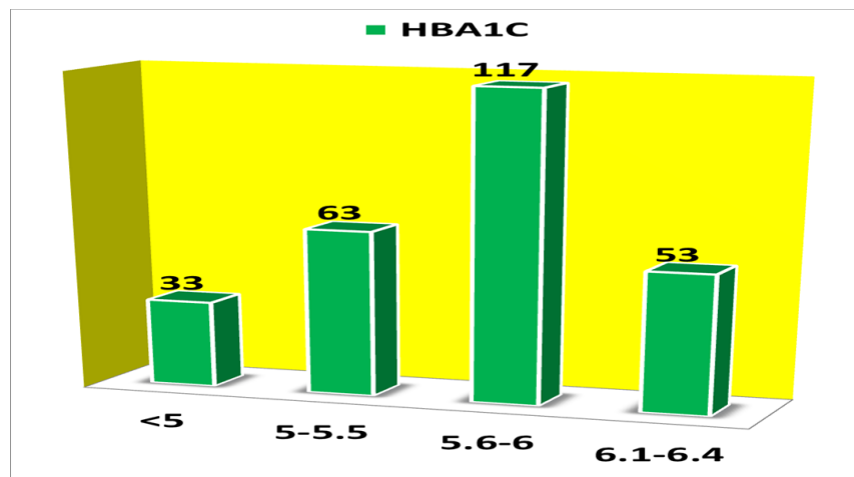
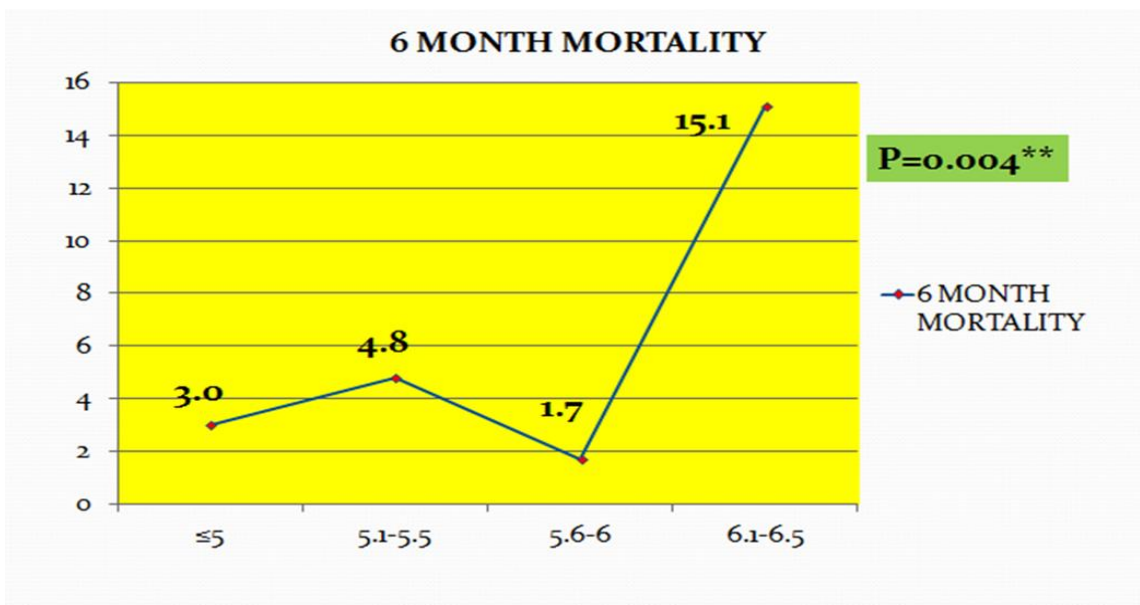**Figure 1:** HBA1C distribution (n=266) in quartiles

Figure 2: HBA1C quartiles subgroup analysis in study population for 6 month mortality (X axis showing HBA1C values, Y axis showing 6 month mortality frequency.)

Discussion:

This is one of the first studies from south India, where correlation between HbA1c level and short term mortality in non-diabetic STEMI patients is attempted. Several studies have reported associations between chronic hyperglycaemia and cardiovascular disease in both diabetic and non-diabetic individuals. Selvin et al [1] and Khaw et al [7] reported that elevated HbA1c levels predict cardiovascular disease and mortality in patients without diabetes, indicating that even milder abnormalities of glucose control below the diagnostic threshold of diabetes mellitus also pose a risk of development of cardiovascular disease. In the community-based Atherosclerosis Risk in Communities study[8] that involved non-diabetic participants, baseline HbA1c levels of 5.5% to less than 6.0%, 6.0% to less than 6.5%, and 6.5% or greater were associated with increasing risk of the development of coronary heart disease compared with those with HbA1c levels of 5.0% to 5.5%. Our findings are in accordance with the results of most of these studies. In our study population, increasing HbA1c levels were clearly associated with higher cardiovascular risk profile, which explains part of the increased risk. In addition, it is conceivable that the same complex mechanisms that are responsible for the adverse association between overt diabetes and cardiovascular outcome (ie, oxidative stress, protein glycation of the vessel wall, and endothelial dysfunction) also play an active role in chronic hyperglycaemia even in the sub-diabetic range. It is also possible that high baseline HbA1c levels represent patients who are at high risk for developing diabetes in the future, thus increasing the risk of developing CAD. However, because our study was cross-sectional, we were unable to assess this hypothesis. There is enough evidence to conclude that strategies to prevent diabetes also reduce the risk of CVD. Hence, as practiced in patients with diabetes mellitus, an intensive multifactorial approach should be used to prevent CVD in pre-diabetic patients.[9] Trans-professional collaboration between cardiologists and diabetologists and a multifactorial and target-driven approach are highly rewarding.[10] Elevated HbA1c was found to be associated with an increased mortality in non-diabetic subjects suffering an AMI. This finding is similar to the finding in the study by TA Chowdhury et al [11]. In our study HBA1C>6 is identified as an independent predictor of 6 month mortality similar to the study by TA Chowdhury et al [11].

For a wide range of known cardiovascular risk factors, we cannot rule out the possibility of residual confounding variables in this observational study.

Conclusion:

1. A significant correlation exists between HBA1C level in non-diabetic STEMI patients & all-cause mortality at 6 months.
2. HBA1C>6.0 has proven to be an independent predictor of all-cause mortality at 6 months in non-diabetic STEMI patients.

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Conflict of interest:

Authors do not have any conflict of interest.

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