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Research Article

# $HbA_{1C}$: IS IT READY AS A PRIMETIME TOOL FOR PREDICTING MYOCARDIAL INFARCTION?

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**ABSTRACT**
$HbA_{1c}$ is regarded as an independent risk factor for acute myocardial infarction in patients with or without diabetes. However, studies regarding $HbA_{1c}$ and increased risk of acute myocardial infarction (AMI) are scarce. The present study is a case control study in which glycated hemoglobin, fasting and postprandial blood glucose; and fasting lipid profile were estimated in all subjects. Though $HbA_{1c}$ helped distinguish between stress induced hyperglycemia and diabetes mellitus, it failed to predict risk of myocardial infarction. More longitudinal and prospective studies in rural areas of India are needed to establish causal relationship so that $HbA_{1c}$ can be used as a prime time tool in clinical evaluation of myocardial infarction.
**Keywords:** Acute myocardial infarction, Glycated hemoglobin, Blood glucose

## INTRODUCTION

The current scenario puts coronary heart disease as one of the leading killers globally. The pooled estimates from studies conducted in India from 1990's till 2002 show that the prevalence rate of MI in urban areas is around 6.4 percent and 2.5 percent in rural areas.[1] The increasing incidence of acute coronary syndromes (ACS) in Indians may be related to the changes in the lifestyle, the westernization of the food practices, the increasing prevalence of diabetes mellitus and probably genetic factors.[2] The importance of identifying risk factors and initiating suitable strategies for prevention of myocardial infarction and cardiovascular risk reduction needs to be stressed upon. Studies suggest that traditional cardiovascular risk factors such as smoking, diabetes mellitus, hypercholesterolemia and hypertension alone do not account for the excess of cardiovascular morbidity and mortality in the non – diabetic population. Several investigations as well as prospective studies have shown a significant correlation between glucose metabolism and cardiovascular disease outcome in patients with or without diabetes.[3,4] From this it can be construed that non-traditional risk markers also should be considered for myocardial infarction risk assessment. Several investigations as well as prospective studies have shown a significant correlation between glucose metabolism and cardiovascular disease outcome in patients with or without diabetes.[3,4] Elevated levels of glycated hemoglobin have been found to be associated with raised atherosclerotic lesions and fatty streaks in coronary arteries.[5] Glycation is the non-enzymatic addition of a sugar residue to amino groups of proteins. Human adult hemoglobin (Hb) usually consists of HbA (97 %), $HbA_2$ (2.5 %) and HbF (0.5 %). Chromatographic analysis of HbA identifies several minor hemoglobins, namely $HbA_{1a}$, $HbA_{1b}$ and $HbA_{1c}$ which are collectively referred to as $HbA_1$, fast hemoglobins, glycohemoglobins or glycated hemoglobins.[6] Studies conducted by Myint PK *et al*, it was observed that $HbA_{1c}$ > 7 % was associated with increased risk of stroke even in the non-diabetics.[7] Even though the etiopathogenesis are considered same for both myocardial infarction and stroke it is not exactly true with respect to $HbA_{1c}$ and myocardial infarction. In the EPIC-NORFOLK study, the possibility of using glycated hemoglobin as an independent predictor of death from cardiovascular disease was explored for the first time by Khaw KT *et al*.[8] These findings prompted the hypothesis that $HbA_{1c}$ could be considered to be an independent and crucial cardiovascular risk factor both in patients with or without diabetes.

## MATERIALS AND METHODS

The present study is a case control study. The study group was selected from inpatients of RL Jalappa hospital and RL Jalappa Narayana Hrudayalaya Critical Care Unit. The control group was of same age and gender matched individuals irrespective of their diabetic status. This study included 106 subjects (cases-51 and controls-55) within a span of one year from February 2012 to July 2013. The study population comprised of men and women in the age group of 30-80 years. The study was divided into groups as follows:
Group I – Acute myocardial infarction cases irrespective of their diabetic status
Group II – Acute myocardial infarction cases with diabetes mellitus
Group III – Acute myocardial infarction cases without diabetes mellitus
Group IV – Controls irrespective their diabetic status
Group V – Controls with diabetes mellitus
Group VI – Controls without diabetes mellitus

### Study group

Inclusion criteria

- Clinically proven cases of myocardial infarction in the age group of 30-80 yrs admitted in R L Jalappa Hospital and Research Centre and RL Jalappa Narayana Hrudayalaya -CCU, Kolar, India.
- Patients with MI were included in this study irrespective of the history of diabetes mellitus.

Exclusion criteria

Patients with thyroid disorders, hemoglobinopathies, pregnancy and severely lipemic samples were excluded from this study because it may lead to altered $HbA_{1c}$ levels.

**Controls**

- Included age and gender matched volunteers with no history of coronary heart disease.
- After considering the inclusion and exclusion criteria the controls were selected accordingly.
- Control group was screened for the same parameters which are done for cases.

**Method of collection of data**

After obtaining informed consent from both cases and control groups, an overnight of minimum 8 h fasting blood was collected for estimation of plasma glucose, serum lipid, calcium and magnesium. Fasting or post prandial whole blood for $HbA_{1c}$ because values are not going to get altered. Post prandial plasma glucose was estimated in the 2 h post prandial blood sample. Universal precautions were taken while collecting the blood samples. Biochemical parameters were done using suitable sample and specific methods-

- Estimation of $HbA_{1c}$ was done by using whole blood mixed with lysing reagent to prepare a hemolysate and was analysed using weakly binding cation exchange resin and by using colorimeter at wavelength ($\lambda$) = 415 nm.[9]
- Plasma glucose was estimated by glucose oxidase and peroxidase method using dry chemistry analyzer –Vitros 250, from Johnson and Johnson.[10]

Since lipid profile is known to get altered due to non-fasting. Fasting lipid profile was done in Vitros 250 dry chemistry auto analyzer from Johnson and Johnson.

- Total cholesterol[11]
- Triglycerides[12]
- HDL cholesterol[13]

Calculated parameters

- LDL cholesterol by Friedewald's formula[14] LDL = TC-[(TG/5)+HDLc]
- Non-HDLc =[TC- HDLc][15]

**Statistical analysis**

The data collected was tabulated and analyzed using descriptive statistical tools- mean, standard deviation and comparison between the groups was carried out by using independent student 't' test and Mann Whitney 'U' test. Complete analysis was carried out using SPSS package evaluatory version 14. 'p' value less than 0.05 was considered statistically significant.

## RESULTS

The cases comprised of 45 males and 06 females, showing a male preponderance with a male: female ratio of 15:2. The mean age was 57.19 ± 10.71 years (range 30-80 years), suggesting an increased trend of AMI with advancing age and included 23 diabetics, 28 non-diabetics. Among the diabetics 19 were males and 04 females. The occurrence of STEMI (64.7 %) was more than NSTEMI (35.3 %) as shown in Figure 1. There was an increased risk of AMI in smokers (54.9 %) than non-smokers (45.1 %) (Odds Ratio 3.24, 95 % Confidence Interval 1.4439 to 7.2988) ($p < 0.05$) as shown in Figure 2. The mean value of $HbA_{1c}$ in AMI patients was 7.52 ± 1.56 % in comparison to 7.59 ± 1.33 % in controls. In the subgroup analyses, in the diabetic AMI group the mean was 8.63 ± 0.99 % and 8.79 ± 0.9 % in controls. In the non-diabetic AMI group the mean was 6.6 ± 1.33 % and 6.67 ± 0.74 % in controls Figure 3. The fasting blood glucose levels were significantly increased in non-diabetic AMI patients 95 ± 17.54 mg/dl compared to non-diabetic controls 84.77 ± 9.92 mg/dl ($p < 0.05$) [Table 3]. It was observed that $HbA_{1c}$ was not significantly elevated in AMI irrespective of diabetic status and also in subgroup analyses of diabetics and non-diabetics. This finding corroborates with that observed in other studies implying that $HbA_{1c}$ is a predictor of chronic glycometabolic state rather than independent risk factor of AMI.[16,17] In the lipid profile significance was found with respect to HDLc only which was significantly decreased when compared to controls. The mean value of serum HDLc in AMI group was 35.94 ± 8.81 mg/dl and 41.1 ± 8.46 mg/dl in controls ($p < 0.05$) [Table 1]. In the subgroup analyses, in the diabetic AMI group the mean was 34.39 ± 8.43 mg/dl and 38.91 ± 6.56 mg/dl in controls ($p < 0.05$) [Table 2]. In the non-diabetic AMI group the mean was 37.21 ± 9.06 mg/dl and 42.8 ± 9.44 mg/dl in controls [Table 3]. These findings are on par with that of Huxley RR *et al* who demonstrated that isolated low HDLc had increased risk of cardiovascular disease.[18]

## DISCUSSION

Acute myocardial infarction (AMI) is leading cause of death among non-communicable diseases in both developing and developed nations. Even in the rural population in India there is an increasing trend of the non-communicable diseases-diabetes mellitus and MI due to sedentary life style and habits. In our study there was a male preponderance observed and the male: female ratio was 15:2. Males in this area are prone for AMI. The mean age was 57.19 ± 10.1 years suggesting there was an increased risk of myocardial infarction with advancing age affecting them in their "golden years of life". The mean age in males with AMI was 57.3 ±10.63 years and in females with AMI the mean age was 56 ± 9.38 years. The core issue of glycated hemoglobin found to be elevated even in non-diabetics with myocardial infarction was addressed in our study. Studies conducted by Pasupathy *et al* to study the combinational effect of cardiac and biochemical markers in diabetic patients with cardiovascular disease, it was observed that the fasting plasma glucose level and glycosylated hemoglobin ($HbA_{1c}$) were elevated in cardiac patients with and without diabetes compared to healthy subjects.[19] However, in our study conflicting results were obtained with respect to $HbA_{1c}$ which was not altered in AMI. This finding of lack of association of admission $HbA_{1c}$ with cardiovascular risk is on par with the findings of Su G *et al*, who observed that admission glycemic variability was a strong predictor of major adverse cardiac events (MACE) but not admission $HbA_{1c}$.[16] Studies conducted by Rasoul S *et al*, showed that among 30 day survivors neither admission glucose nor $HbA_{1c}$ were predictors of long term mortality.[17] In our study we observed that fasting blood glucose levels were significantly elevated in non-diabetic AMI patients than controls, 95 ± 17.54 mg/dl and 84.77 ± 9.92 mg/dl respectively ($p < 0.05$). The DECODE Study group observed that slightly elevated glucose levels, even in the non-diabetic range, might be associated with increased cardiovascular disease risk.[20] In the Northern Sweden MONICA project which, in turn, is a part of the WHO MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease) it was shown that in women with impaired glucose

tolerance the risk of silent MI was more than men.[21] However, in our study there was a male preponderance. The mean age in males with AMI was 57.3 ± 10.63 years and in females with AMI the mean age was 56 ± 9.38 years. There was not much difference in age. In AMI patients 54.9 % were smokers and consumed tobacco all were males and the female patients did not have the habit of tobacco chewing. Hence, tobacco exposure could be the predisposing factor in males in our study. In our study, fasting blood glucose in non-diabetics is not only a marker of glucose dysregulation but also increased cardiovascular disease risk probably due to the elevated free fatty acids and increased thrombotic properties of platelets, enhanced oxidative stress, the activation of blood coagulation and platelets, stimulation of inflammation, and endothelial cell dysfunction. Lipid profile is a traditional marker of increased cardiovascular disease risk. However, in our study the total cholesterol, triglycerides, LDL and non-HDLc were not significantly increased in AMI patients irrespective of their diabetic status albeit HDL cholesterol which was significantly decreased in AMI patients both diabetics as well as non-diabetics when compared to controls ($p < 0.05$). Serum lipids are known to decrease 24 hours following acute myocardial infarction and remain so for 2-3 months. The probable mechanisms are metabolic effect of stress, hormones, increased LDL receptor activity and increased cholesterol catabolism.[22] The findings of our study suggest that glycated hemoglobin is elevated in clinically advanced diabetes mellitus and its association with myocardial infarction may be due to coexistent traditional risk factors.

**Table 1: Comparison of Parameters between Acute Myocardial Infarction Cases (Group I) and Controls (Group II) Irrespective Of Their Diabetic Status by Student 'T' Test**

| Parameter | Group I (n = 51) Mean ± SD | Group IV (n = 55) Mean ± SD | 'p' value |
|---|---|---|---|
| FBS (mg/dl) | 132.22 ± 64.24 | 115.04 ± 53.88 | 0.138 |
| PPBS (mg/dl) | 161.86 ± 92.48 | 162.8 ± 89.32 | 0.958 |
| $HbA_{1c}$ % | 7.52 ± 1.56 | 7.59 ± 1.33 | 0.79 |
| Total cholesterol (mg/dl) | 163.9 ± 40.08 | 172.5 ± 36.81 | 0.253 |
| Triglycerides (mg/dl) | 145.59 ± 83.64 | 148.87 ± 58.61 | 0.814 |
| HDL (mg/dl) | 35.94 ± 8.81 | 41.1 ± 8.46 | <0.05* |
| LDL (mg/dl) | 100.64 ± 32.92 | 101.6 ± 31 | 0.878 |
| Non – HDL (mg/dl) | 127.04 ± 39.94 | 131 ± 35.8 | 0.592 |

*Statistically significant; **Strongly significant

**Table 2: Comparison of Parameters between Acute Myocardial Infarction with Diabetes Mellitus (Group II) and Controls (Group V) By Mann Whitney 'U' Test**

| Parameter | Group II (n = 23) Mean ± SD | Group V (n = 24) Mean ± SD | 'p' value |
|---|---|---|---|
| FBS (mg/dl) | 177.52 ± 71.37 | 154.12 ± 62.1 | 0.263 |
| PPBS (mg/dl) | 230.39 ± 100.62 | 240.5 ± 85.88 | 0.573 |
| $HbA_{1c}$ % | 8.63 ± 0.997 | 8.79 ± 0.9 | 0.22 |
| Total cholesterol (mg/dl) | 157.96 ± 37.32 | 172.8 ± 32.24 | 0.17 |
| Triglycerides (mg/dl) | 145.87 ± 95.46 | 154.96 ± 48.6 | 0.221 |
| HDL (mg/dl) | 34.39 ± 8.43 | 38.91 ± 6.56 | <0.05* |
| LDL (mg/dl) | 96.45 ± 31.61 | 102.7 ± 32.19 | 0.468 |
| Non – HDL (mg/dl) | 122.65 ± 37.25 | 133.17 ± 33.87 | 0.278 |

*Statistically significant; **Strongly significant

**Table 3: Comparison of Parameters between Acute Myocardial Infarction without Diabetes Mellitus (Group III) and Controls (Group VI) By Mann Whitney 'U' Test**

| Parameter | Group III (n = 28) Mean ± SD | Group VI (n = 31) Mean ± SD | 'p' value |
|---|---|---|---|
| FBS (mg/dl) | 95 ± 17.54 | 84.77 ± 9.92 | <0.05* |
| PPBS (mg/dl) | 105.5 ± 17.45 | 102.65 ± 11.71 | 0.704 |
| $HbA_{1c}$ % | 6.6 ± 1.33 | 6.67 ± 0.74 | 0.308 |
| Total cholesterol (mg/dl) | 168.8 ± 42.25 | 172.2 ± 40.53 | 0.773 |
| Triglycerides (mg/dl) | 145.36 ± 74.3 | 144.1 ± 65.73 | 0.849 |
| HDL (mg/dl) | 37.21 ± 9.06 | 42.8 ± 9.44 | <0.05* |
| LDL (mg/dl) | 103.92 ± 34.12 | 100.68 ± 30.55 | 0.693 |
| Non – $HDL_c$ (mg/dl) | 130.64 ± 42.34 | 129.32 ± 37.69 | 0.873 |

*Statistically significant; **Strongly significant

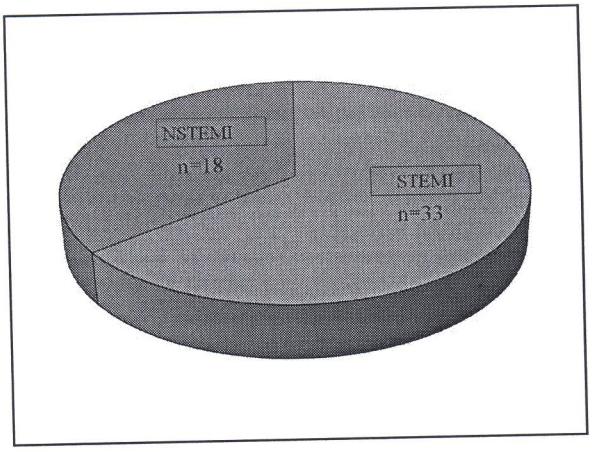


**Figure 1: Distribution of Types of AMI**

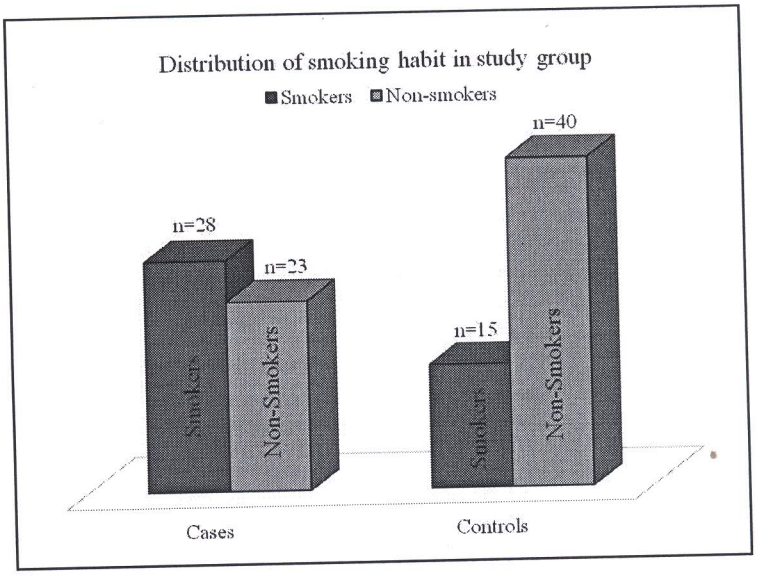


**Figure 2: Distribution of Smoking Habit in Study Group (Total Cases and Controls)**

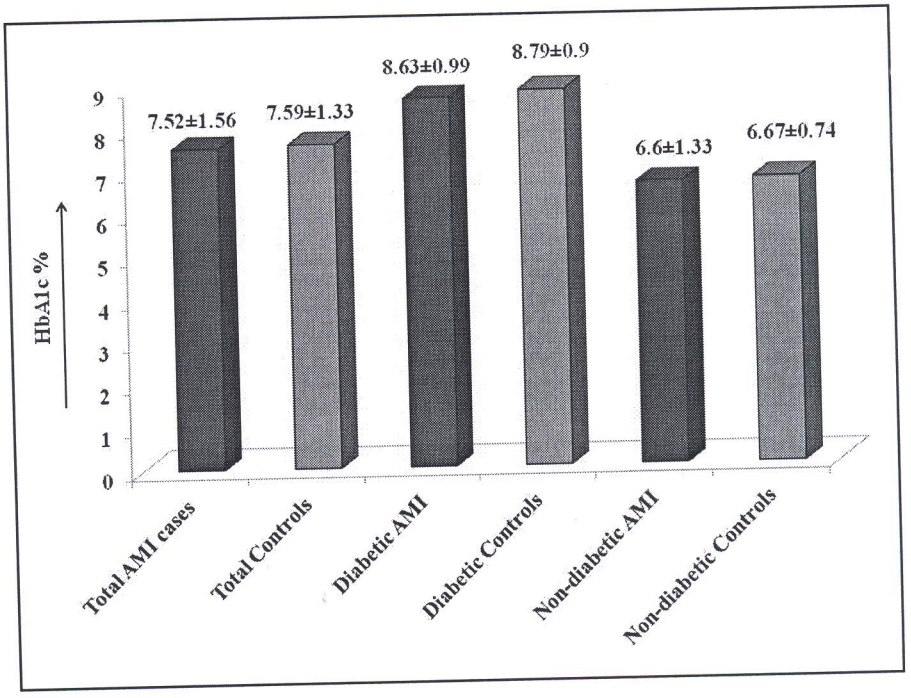


**Figure 3: Comparison of $HbA_{1c}$ Levels in Various Groups**

## CONCLUSION

Admission $HbA_{1c}$ levels in acute myocardial infarction is a useful inexpensive test for differentiating between stress induced hyperglycemia and diabetes mellitus. $HbA_{1c}$ failed to predict risk of myocardial infarction. More longitudinal and prospective studies in rural areas of India are needed to establish causal relationship so that $HbA_{1c}$ can be used as a prime time tool in clinical evaluation of myocardial infarction. Elevated fasting blood glucose in non-diabetics is not only a marker of glucose dysregulation but also increased cardiovascular disease risk. Isolated low HDL cholesterol is a new lipid phenotype with increased myocardial infarction and in these individuals with isolated low HDLc rather than lipid lowering therapies, smoking cessation and life style modification would prove beneficial.

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