A STUDY OF GLYCOSYLATED HEMOGLOBIN (HbA1c) IN ACUTE CORONARY SYNDROME

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ABSTRACT

Background: In non diabetic patients, HbA1C could be utilised for risk stratification of CAD and its severity; independent of traditional cardiovascular risk factors.

Objectives: To study the blood levels of HbA1C in patients of ACS at time of admission and its relation with early outcome and complications in ACS.

Method- A total of 100 indoor patients without known diabetes, with confirmed diagnosis of ACS are included in study. HbA1C was done along with other routine investigations. Coronary Angiography was performed in all patients.

Results-Out of 44 patients with HbA1C value > 6.5%, 20 (45.5%) had Anterior wall (A/W) MI, 15(34.1%) had Inferior wall (I/W) MI, 2 (0.05%) had Lateral wall (L/W) MI, 5(11.4%) had NSTEMI and 1 (0.02%) had UA. While of 56 patients with HbA1C value < 6.5%, 19 (33%) had A/W MI, 18 (32.1%) had I/W MI, 5 (0.09%) L/W MI, 2 (0.04%) had NSTEMI and 12 (21.4%) had UA. Out of 88 patients with normal RBS on admission, 33 patients had HbA1C > 6.5% i.e. in diabetic range. 31.8% of patients of raised HbA1C had complicated MI while complication rate in normal HbA1C group was 14.3% only.

Conclusion- Patients with high HbA1C levels were associated with more severe disease and complication rate was also higher.

Key words Glycated Hemoglobin (HbA1C), Acute coronary syndrome(ACS), Random blood sugar.

INTRODUCTION

Concomitant occurrence of hyperglycemia in patients presenting with ACS(Acute coronary syndrome) enhances the risk of mortality and morbidity, whether the patient has diabetes or not.[1]Among patients presented with ACS with no prior history of diabetes, hyperglycemia may reflect previously undiagnosed diabetes, stress-related carbohydrate intolerance, or a combination of these. Several studies have reported an association between elevated blood glucose upon admission and subsequent increased adverse events, including congestive heart failure, cardiogenic shock and death.[2,3,4]

Thus stress hyperglycemia in non-diabetic patients and uncontrolled blood sugar in diabetic patients both are having adverse prognostic effects in patients of ACS. However the effect of recently elevated blood sugar as measured by HbA1C has still not been consistently reported as a bad prognostic indicator. Though many studies have been done[2,3,4] on this interesting subject, the results are not significantly conclusive on either side.

Available data suggests that hyperglycemia on admission is an indicator of short term mortality in patients admitted with acute myocardial infarction but whether it can predict the long term mortality with same efficacy is still not clear.[4]

It has been observed among patients with high risk non ST elevation acute coronary syndrome [NSTE

ACS] that a substantial proportion of patients admitted with high risk NSTE ACS had previously undiagnosed DM (12.2%) or prediabetes (10.8%) as defined by HbA1C or FBS after admission.[5]

In population based studies, including diabetic and nondiabetic cohorts, HbA1C has been reported as an independent predictor of all cause and cardiovascular disease mortality.[5] In nondiabetic patients, HbA1C could be utilised for risk stratification of CAD and its severity; independent of traditional cardiovascular risk factors.[6]

The role of HbA1C has been established in diagnosis of DM and in therapeutic decision making. However the impact of HbA1C levels in early & late outcome of ACS is yet to be established.

That is why we thought it worthwhile to get first hand information of effects of HbA1C levels on early outcome of ACS. This being a short duration non comparative study with a small sample size, the results may not be extrapolated at large to general population.

AIMS AND OBJECTIVES

Present study has been aimed to find out relationship of HbA1C levels in early outcome of ACS patients. We carried out the study with the objectives to elucidate possible association between HbA1C and admission glucose identified during the initial hospitalization; to find out the prevalence of impaired glucose tolerance and type 2 diabetes in study population without previously diagnosed diabetes; and to find out the relation between levels of HbA1C & complication / outcome of ACS.

MATERIAL AND METHOD

A total of 100 patients with Acute Coronary Syndrome without prior history of DM who received in patient care at our tertiary care hospital,. Following are the inclusion and exclusion criteria.

Inclusion criteria: All patients admitted to the hospital with ACS not having diabetes as a past medical history were included in the present study. ACS was diagnosed by criteria: 1) Anginal chest pain within 6 hours before admission; and 2) Typical ECG changes like ST elevation myocardial infarction, NSTEMI or Unstable angina(UA).

Exclusion criteria: Patients having history of past or present diabetes with or without history of anti diabetic drugs were excluded from the study. Further exclusion criteria are angina secondary to extra-cardiac causes. e.g. anaemia, thyroid disease; treatment history of drugs those alter HbA1C levels (Dapsone, Antiretroviral, Vitamin C, Vitamin E etc)[7]; Renal failure or Nephrotic syndrome; hemoglobinopathies; pregnancy; age < 18 yrs; systemic inflammatory response syndrome; and post Myocardial Infarction-Angina.

A total of 100 patients without known diabetes, with confirmed diagnosis of ACS and satisfying the inclusion &exclusion criteria were included in study group.

Detailed clinical history and thorough physical examination was carried out in all patients. All routine investigations, fasting serum lipid profile and chest X ray were done after emergency treatment is given.

HbA1C (Glycosylated haemoglobin) - On admission HbA1C level was detected in each patient. HbA1C < 6.5% was considered normal while >6.5% was considered raised. All the patients were followed up daily to find out development of any complication and finally at the time of discharge from the hospital.

Coronary angiography was performed in all patients and disease severity was classified as SVD, DVD & TVD.

PEEL'S index[8] for severity of CAD was calculated in each patient. Interpretation of PEEL'S index:

Index range	Expected mortality (%)
1-8	3
9-12	12
13-16	24
17-20	54
> 20	88

Total index ranges from 1 to 28.

The observations of all 100 patients were recorded and a master chart of all 100 patients was prepared. The relevant data was analysed by using word-excel software.

OBSERVATION

This study included 100 adult previously non diabetic patients (80 males and 20 females).

Table 1-Age & gender distribution:

Age	Male (n=80) (%)	Female (n=20) (%)	Total (n=100) (%)
< 40yrs	7 (87.5%)	1 (12.5%)	8 (8%)
40-59 Yrs	41 (85.41%)	7 (14.58%)	48 (48%)
60-79 Yrs	28 (73.68%)	10 (26.31%)	38 (38%)
>80 Yrs	4 (66.66%)	2 (33.33%)	6 (6%)

Table 2-Type of ACS based on ECG criteria

ACS	Male (n=80) (%)	Female (n=20) (%)	Total (n=100) (%)

STEMI	69 (86.25%)	11(13.75%)	80 (80%)
NSTEMI	5 (71.42%)	2 (28.57%)	7 (7%)
UA	6 (46.15%)	7 (53.84%)	13 (13%)

p value by Fischer's exact test is 0.0039

Table 3-Relationship between HbA1C and certain clinical and laboratory variables

Variables	HbA1C			P value
	< 6.5% (n=56)	>6.5% (n=44)	Total (n=100)	
Type of ACS				
STEMI	42 (75)	38 (86.36)	80 (80)	0.21
NSTEMI	2 (3.5)	5 (11.36)	7 (7)	
UA	12 (21.42)	1 (2.27)	13 (13)	
RBS				
> 200 mg/dl	1 (8.3)	11 (91.66)	12 (12)	0.0004
<200 mg/dl	55(62.5)	33 (37.5)	88 (88)	
FBS				
> 126 mg/dl	4 (17.39)	19 (82.6)	23 (23)	<0.001
< 125 mg/dl	52 (67.53)	25 (32.46)	77 (77)	
RBS >200 mg/dl **&FBS > 126** mg/dl	1	10	11	

Table 4-Relationship between complications of MI and HbA1C:

Complications of MI	HbA1C		Total
	<6.5%	**> 6.5%**	
Arrhythmia	3 (13.63)	9 (40.90)	12 (54.54)
LVF	3 (13.63)	1 (4.54)	4 (18.18)
Mortality	0	3 (13.63)	3 (13.63)
Others	2 (9.09)	1 (4.54)	3 (13.63)
Total	**8(36.36)**	14(63.63)	22

P value is 0.0318.

Table 5: Relation between severity of disease and HbA1C

Severity of disease	HbA1C		Total
	<6.5%	**> 6.5%**	
SVD (single vessel ds)	45 (46.39)	20 (20.61)	65 (67.01)
DVD (double vessel ds)	11(11.34)	19 (19.58)	30 (30.92)
TVD (triple vessel ds)	0	2 (2.06)	2 (2.06)
Total	56 (57.73)	41 (42.26)	97

P value is 0.0011

Table 6- Relation between Peel's Index and HbA1C

Peel's index[8]	HbA1C		Total
	<6.5%	**> 6.5%**	
01-12	54 (96.4)	37 (84.1)	92 (92.0)
13-20	2 (3.6)	7 (15.9)	8 (8.0)
Total	56	44	100

The Fisher exact test applied. P value is 0.040

Youngest patient in our study was 27 years old while the oldest patient was 100 years old and mean age was 55.73±12.69. Maximum number of patients was in the age group of 40-59 years. M: F ratio in present study was 4:1

As per ECG criteria we found out that of 80 patients of STEMI consisting of 51 males and 5 females, 19 (16 males & 3 females) were of anterior wall MI & 18 (16 males & 2 females) were of inferior wall MI forming major bulk of the patients.

Out of 44 patients with HbA1C value > 6.5%, 20(45.5%) had Anterior wall (A/W) MI, 15(34.1%) had Inferior wall(I/W) MI, 2(0.05%) had Lateral wall(L/W) MI, 5(11.4%) had NSTEMI and 1(0.02%) had UA. While of 56 patients with HbA1C value < 6.5%, 19(33%) had A/W MI, 18(32.1%) had I/W MI, 5(0.09%) L/W MI, 2(0.04%) had NSTEMI and 12(21.4%) had UA.

At the same time i.e. on admission RBS was also measured and it was found to be normal in 88%. Of these 88 patients 33 had HbA1C > 6.5% i.e. in diabetic range.

Thus 37.5% of patients of normal RBS did have hyperglycemia on or before development of MI. FBS (fasting blood sugar) was normal in 77% of patients in which group, 25 had elevated HbA1C.

Amongst those having HbA1C >6.5, 8 patients were of STEMI (5 A/W and 3 I/W MI) and 3 were of NSTEMI.1 patient of UA had raised HbA1C but had RBS(Random blood sugar) of 320 and FBS of 256.

Of 100 patients we studied, 3 patients died. All 3 had severely raised (>8) HbA1C, TVD (triple vessel disease) and higher peel's index (7, 17, 14).

While 19 others developed complications like Left ventricular failure(LVF), arrhythmia, cardiogenic shock etc. While correlating levels of HbA1C in patients who developed complication of MI we observed following:

It was also observed that 31.8% of patients of raised HbA1C had complicated MI while complication rate in normal HbA1C group was 14.3% only. We did observe that the patients with complicated MI had not only higher HbA1C but levels were also higher i.e. >8.5%

Severity of ACS was determined clinically by PEEL's index as well as by angiography.PEEL's index was calculated in each patient. Mean value was 6.43. Coronary angiography was also performed in all patients (except for 3 patients in whom mortality has occurred).

Only 2 patients had TVD and both have raised HbA1C levels, while from 30 patients of DVD 19 were found to have HbA1C > 6.5 and more patients with normal HbA1C were found to have SVD.

We could observe that HbA1C levels were higher in the patients with higher index and complication rate was also higher.

DISCUSSION

We studied 100 non diabetic ACS patients to observe the predictive rate of HbA1C with relation to early complication and severity of disease. Stress hyperglycemia is a known marker and predictor for severity & complications of ACS. We tried to establish the accuracy and superiority of HbA1C over random blood sugar.

According to suzzane et al[9] underlying diabetes mellitus (DM) that has not been previously diagnosed is common among acute myocardial infarction (AMI)patients affecting 1 in 10 patients. HbA1C testing should be considered for screening of all AMI patients for DM.

We observed that all these patients who died during hospital stay had very high values of HbA1C (8.0, 8.6 &10.9) and severe disease as indicated by their Peel's index. However the no of patients (3) is too low to derive statistical significance and further studies with larger sample size would be needed to establish this relation. However in all these patients had blood sugar (RBS & FBS) levels also raised and thus specificity and sensitivity of HbA1C cannot be established.

We did review other related studies and found that demographic data, age & gender distribution and percentage of patients with high HbA1C levels were compatible with other studied as shown below.

In present study 56(56%) patients were having HbA1C < 6.5 out of which 44 patients were male and 12 patients were female and 44 (44%) patients were having HbA1C > 6.5 out of which 36 patients were male and 8 patients were female. While in Cakmaket al[10] study 25% patients were with HbA1C < 6.5 out of which 11 patients were male and 14 patients were female and 75% patients were with HbA1C > 6.5 in which there were 57 males and 18 females. In Rasoul et al[4]study 82.50% patients were with HbA1C < 6.5 and 17.50% patients were with HbA1C > 6.5.

While correlating severity of disease and HbA1C levels in present study we found that more number of patients with severe disease i.e. double and triple vessel disease had higher levels of HbA1C while more patients amongst of single vessel disease had lower levels of HbA1C, Similar relation has been observed by Cakmak et al[10] also. Thus stress hyperglycemia has been found to be associated with severity of the disease, but it is not necessary that only HbA1C is required. Similar predictive values have been found by correlation with RBS and FBS/PPBS also.

Vinita etal[11] has mentioned that the correlation between higher HbA1C levels and increased cardiovascular mortality occurs even before the diagnosis of clinical diabetes. Our results also indicate the same fact.

Maximum number of patients with RBS >200 and FBS >126 on admission were also having HbA1C > 6.5.

Essays of HbA1C levels though now easily available in almost all major laboratories, its cost is about 600 INR and this may not be available at district & village level. Under these circumstances when RBS had similar predictive values we do not recommend inclusion of HbA1C as a standard protocol of investigation in patients of ACS.

Mean HbA1C level of all non diabetic patients was 6.7%.It is well known that the macro vascular complications start taking place at lower blood sugar levels than the diagnostic cut off values for diabetics. Khawet al[12] found a continuous and significant relationship between HbA1C, cardiovascular events and all cause mortality, whereby persons with HbA1C < 5% had lowest rates of cardiovascular disease and mortality. A 1% increase in absolute concentrations of glycated haemoglobin is associated with about 10-20% increase in cardiovascular disease risk.

Among patients with HbA1C < 6.5,maximum number of patients were having single vessel disease which correlates well with Cakmak et al[10] study which found 21, 3 and 1 patient with single, double and triple vessel disease respectively.

Among patients with HbA1C > 6.5%, more number of patients were with double and triple vessel disease. In Cakmaket al[10] study 21, 22 and 35 patients were with single, double and triple vessel disease respectively.

In Rasoulet al[4] study comprising of 504 total patients 416 had HbA1C < 6, amongst which 62% had SVD and 38% had DVD or TVD or more severe disease. While of 88 patients with HbA1C > 6, 44% had SVD and 66% had DVD or TVD or more severe disease clearly suggesting that raised HbA1C levels are associated with severe disease.

According to Ghaffari S et al[13] study among nondiabetic patients presenting with STEMI, the severity of CAD was higher in those with HbA1C level>5.8%, 1 year mortality and hospital readmission rates were also higher.

Mortality: In Rasoulet al[4] study 5% mortality is noted in those having HbA1C <6 which was found to be 12% in those having HbA1C >6 at 30 days of

follow up. In Cakmaket al[10] study 7% patients died during the course of next 28 days and in present study 3 patient died during next 48 hrs. In Timmer JR[14] et al study HbA1C was independently associated with long term mortality.

CONCLUSION

HbA1C> 6.5 in patients of acute coronary syndrome is associated with more complication rate, high mortality as well as angiographically more severe disease. Raised HbA1C level (> 6.5) was found in 44 out of 100 previously non diabetic patients with acute coronary syndrome. In present study we could not find any superiority of HbA1C in predicting outcome of ACS over blood sugar. However the sample size in each group in present study was not very large and we think that further study with larger sample size and comparative design may further clarify the value of HbA1C in ACS.

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