Original Research Article

Evaluation of Glycated Hemoglobin (HbA1c) in Acute Coronary Syndrome (ACS)

Abstract:

Aim: The aim of our study was to estimate the level of HbA1c in patients with Acute Coronary Syndrome (ACS). To determine any correlation between HbA1c, admission blood glucose (Random blood sugar), serum lipid profile among the cases and to evaluate the outcome during hospitalization.

Study design and setting: Cohort study.

Place and Duration of the Study: Department of Biochemistry and General Medicine including ICCU and Cardiology unit, RIMS, Imphal, between September 2015 to August 2017.

Methodology: Data were collected from 98 patients admitted in Medicine ward who were diagnosed with ACS irrespective of their diabetes status and they were divided into three groups according to their HbA1c levels (<5.7%, 5.7-6.4%, > 6.5%). The blood samples collected by venipuncture were analyzed for HbA1c level, done by RANDOX HbA1c Rx series (latex agglutination inhibition assay), admission blood glucose (measured by Trinder's method) and serum lipid profile (RANDOX enzymatic Endpoint Method Rx series). The data were analyzed using statistical tools like Chi Square test, Independent sample t test, Pearson's Correlation, Fisher's exact test through SPSS 21.0.

Results: Majority of the patients were men (72.4%) & (27.6%) women and in the age group of 51-65 years. The mean age is 62.14 years. 54.1% of the ACS patients were already diagnosed cases of type 2 diabetes mellitus whereas 45.9% were non-diabetic. Out of 98 patients, 60 had HbA1c level in the diabetic range (≥6.5%), 25 in the pre-diabetic range (5.7-6.4%) and the remaining 13 were within normal range (<5.7%). Admission blood glucose, total cholesterol and LDL were positively correlated with HbA1c value.

Conclusion: The mortality of the ACS patients irrespective of diabetic status during hospitalization was associated with HbA1c value irrespective of diabetic status during hospitalization. However, it was not associated with thirty days mortality.

1. INTRODUCTION

Cardiovascular disease (CVD) remains a major contributor to morbidity and mortality in the unites states and worldwide. Ischemic Heart Diseases (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. Patients with IHD fall into two groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina and patients with acute coronary syndromes (ACS) which can ultimately lead to heart attack. [1]

The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100000 population in India is higher than the global average of 235 per 100000 population. [2]

Acute coronary syndrome (ACS) states to a group of conditions that comprise non ST-elevation myocardial infarction (NSTEMI), and unstable angina. It is a type of coronary heart disease (CHD), which is responsible for one-third of total deaths in people older than 35 years. The risk factors are diabetes mellitus (T2DM), male sex, family history of obesity, smoking, physical inactivity, hypertension, hyperlipidemia, and poor nutritional practices. Diabetes is one of the most important risk factors of ACS. In addition, impaired glucose tolerance and impaired fasting glucose, pre diabetes are also important risk factor.[1,3]

The prevalence of diabetes among ACS patients varies between 19.2-37%.[1,3,4] Recent evidence has shown that chronic deregulation, assessed by HbA1c levels, is of prognostic value with regard to future CVD. There are certain studies that suggest that admission blood glucose but not HbA1c predicts short term mortality after ACS. However, it is still uncertain whether glucose dysregulation is associated with poor long-term prognosis. [5]

Glycated hemoglobin (HbA1c) is formed by non-enzymatic glycation of N-terminus of beta chain of hemoglobin. It represents an average blood glucose level over the previous three months. In 2009, The international committee recommended the use of HbA1c to diagnose diabetes mellitus with a threshold ≥ 6.5%. The American diabetes association (ADA) adopted

this recommendation in its position statement entitled, "*standard of medical care in diabetes 2010"*. The diagnosis should be standardized to diabetes control and complication trials (DCCT) reference assay or the National glycohemoglobin standardization program (NSGP) certified method. [6]

The ADA recommended goal for HbA1c is < 7% in all cases of DM. The same level is recommended for primary prevention of CV diseases in people with diabetes.[7] HbA1c values >7% are associated with a significant increase in the risk of cardiac events and deaths. Henceforth assessment of HbA1c, effect on mortality is imp. to improve the prognosis of patients with ACS and to prevent the adverse outcome. Hyperglycemia plays a key role in inhibition of nitrous oxide (NO) production and surplus production of reactive oxygen species (ROS) in endothelium and vascular smooth muscles. This phenomenon is called oxidative stress which may be regarded as a first step in production of atherosclerosis. [8]

Dyslipidemia has been identified as a key role in development of increased risk factor for CVD. It includes hypercholesterolemia, high level of low-density lipoprotein cholesterol (LDL) and low level of high-density lipoprotein cholesterol (HDL) [9] . HDL cholesterol is one of important lipoproteins that has the potential to prevent atherosclerosis by changing the "biology" of arterial wall lesion, without being affected by LDL cholesterol level. LDL-c is an atherogenic lipoprotein and it should be decreased and represents the major cause of CHD.[10 ,11,12] TG may cause higher clearance rate of HDL cholesterol, which finally causes low HDL cholesterol level and leads to endothelial dysfunction[13]. Early intervention and prevention of dyslipidemia can intensely reduce the development of cardiovascular diseases (CVD).

In the current study , we aimed to estimate the level of HbA1c in patients with Acute Coronary Syndrome (ACS), to determine any correlation between HbA1c, admission blood glucose (Random blood sugar), serum lipid profile among the cases and lastly to evaluate the outcome during hospitalization.

2. METHODOLOGY

Ours is a Cohort study. This research project was carried out in Department of Medicine including ICCU and the Cardiology unit, RIMS, Imphal, between September 2015 to August 2017. In the Medicine OPD ninety-eight patients who were admitted with Acute Coronary Syndrome (ACS) were inducted into this study. Convenience Sampling technique was adopted.

5 ml of blood samples was collected from each of the patient. The serum was separated and the following biochemical tests were run: for HbA1c (by RANDOX HbA1c Rx series - latex agglutination inhibition assay) and admission blood glucose measurement (Trinder's method) in EDTA vials. Lipid profile was measured by RANDOX enzymatic Endpoint Method Rx series and blood samples was collected in plain vial.

Apart from biochemical parameters, the anthropometry which included weight and height of patients was also recorded according to standard protocol. The Body Mass Index (BMI) was calculated as weight (kg) divided by the square of the height in meter.

Screening of the patients for the condition of inclusion & exclusion was done.

Inclusion criteria: All patients aged ≥ 18 years admitted with ACS in the Medicine ward or ICCU irrespective of socio-economic status.

Exclusion criteria:

1. Patients with Cardiomyopathy, valvular heart disease, post cardiac surgery, atrial fibrillation, acute stroke and ventricular tachyarrhythmia.

2. Patients with high red cell turnover such as sickle cell disease, G6PD deficiency disease, anemia under iron regime or erythropoietin and auto immune hemolytic anemia.
3. Patients with Chronic kidney diseases on dialysis and chronic liver failure

Statistical analysis:

Data were analyzed using SPSS for windows version 21.0 software. Descriptive statistics were presented in percentages, proportion, mean ± standard deviation. Independent sample t test, Pearson's correlation, and Fisher's exact test value were used wherever found to be suitable and accordingly interpretation was made. The association between HbA1c and selected variables are analyzed by using Chi-square test. Correlations were analyzed using spearman's rank correlation co-efficient (rho). A p-value of less than 0 .05 was considered statistically significant.

3. RESULTS

The present study was conducted on ninety-eight subjects of Acute Coronary Syndrome (ACS) patients irrespective of diabetes or non-diabetes. In order to achieve the objectives of the proposed study important parameters like age, sex, region, admission blood glucose, serum lipid profile, HbA1c have been considered.

Table 1: Socio-demographic characteristics of study group (N=98)

Variables	Number	Percentage
Age in years		
35-50	14	14.5%
51-65	53	54.1%
>65	31	31.6%
Mean ± SD	62.14 ± 12.12	

Sex		
Female	27	27.6%
Male	71	72.4%
Region		
Rural	53	54.1%
Urban	45	45.9%

Table no 1 shows that majority of respondents (54.1%) are in the age-group 51-65 years. Male respondents (72.4%) are more than female respondents (27.6%). Forty-five (45.9%) and fifty-three (54.1%) respondents are from urban population and rural population respectively.

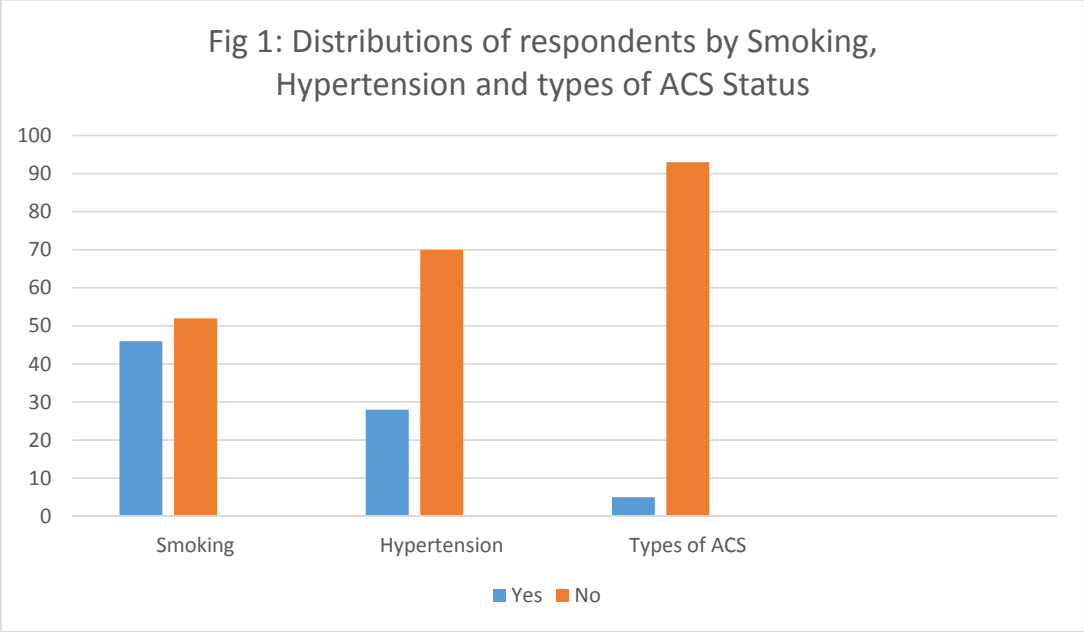

Fig 1: Distribution of respondents by smoking status which shows that most of the respondents are smokers (52%). Among the respondents 71.4 % are hypertensive and 28.6% are non-hypertensive. Most of the ACS cases were diagnosed with STEMI (94.9%) as compared to NSTEMI which were only 5.1% among respondents.

Table 2: Distribution of respondent according to admission glucose (AG) and its association with HbA1c.

Admission glucose(mg/dl)		HbA1c (%)			Total
		<5.7 (n=13) (group 1)	5.7-6.4 (n=25) (group 2)	≥6.5 (n=60) (group 3)	
≥200mg/dl	Count	13	22	28	63
	% within AG	20.6.0%	34.9.0%	44.4%	100.0%

< 200mg/dl	Count	0	3	32	35
	% within AG	0%	8.6%	91.4%	100.0 %
Total	Count	13	25	60	98
	% within AG	13.3%	25.5%	61.2%	100 %

P value = 0.00

Table 2 shows that respondent having HbA1c (5.7-6.4) are found to be more in admission glucose level ≥ 200mg/dl than admission glucose level $< 200mg/dl$. When we look further into it, respondent having AG ≥ 200mg/dl is found to be more in group 2 when we compared with group 1.

Table 3: Association of HbA1c and Diabetes in study respondent

Diabetes	HbA1c			Total
	<5.7% (group1)	5.7-6.4% (group 2)	≥ 6.5% (group 3)	
Yes	0	2	51	53
No	13	23	9	45
Total	13	25	60	98

p value=0.00

Table 3 shows that among the non-diabetes cases, majority of the respondent (51.1%) are in group 2 (HbA1c 5.7-6.4%) whereas among the diabetes cases, most of the respondent (96.2%) are in group 3 (HbA1c≥6.5%) with significant p value of 0.00

Table 4: Demographic and biochemical data of the respondents based on HbA1c levels.

Variables	HbA1c (%)			p value
	<5.7(n=13) (group 1)	5.7-6.4(n=25) (group 2)	≥6.5%(n=60) (group 3)	
Age(years)	60±9.3	60±13.6	63±11.9	0.41
BMI	22±1	22±1	23±2	0.08
AG (Admission glucose)	104.1±17.7	136±39.6	204±70.29	0.00
T. Cholesterol	181.5±52.9	159.4±39.1	185.1±43.7	0.051

Triglycerides	105.3±37	96.8±33	128±39.5	0.001
HDL	55.8±48.7	55.9±26	37.8±16.2	0.004
LDL	94.8±38.5	90.3±39.8	104.7±40	0.28

As shown in Table 4; the mean value of age, BMI, AG, TG and LDL are higher in Group 3 (HbA1c > 6.5%) compared to Group 1 (HbA1c < 5.7%) and Group 2 (HbA1c 5.7-6.4%). It was significant in AG only. Mean HDL is lower in Group 3 as compared to group 1 and 2 and it was significantly observed.

Table 5: Correlation of HbA1c with AG, Cholesterol, Triglycerides, HDL and LDL levels.

Variable	**Correlation coefficient with HbA1c**	**p-value**
AG (admission glucose) mg/dl	0.542	0.000
Cholesterol mg/dl	0.258	0.010
Triglyceride mg/dl	0.188	0.064
HDL mg/dl	-0.195	0.053
LDL mg/dl	0.282	0.005

Table 5 shows significant correlation between AG, cholesterol and LDL with HbA1c except Triglycerides and HDL.

Table 6 : Association of HbA1c level with the outcome among the respondents during hospitalization.

HbA1c level In mg/dl	Outcome		Total (%)	p-value*
	Alive (%)	Death (%)		
<5.7 (group 1)	13 (100)	0 (0.0)	13 (100.0)	
5.7-6.4 (group 2)	25 (100.0)	0 (0.0)	25 (100.0)	
≥ 6.5 (group 3)	51 (85.0)	9 (15.0)	60 (100.0)	**0.011**
Total	89 (90.8)	9 (9.2)	98 (100.0)	

*Fisher exact test

Table 6 shows that 15% of the ACS patients were found to be death in Group 3 (HbA1c>6.5%) as compared with other groups and it was statistically significant.

4. DISCUSSION

Cardiovascular Disease (CVD) is a major cause of decease and disability among diabetes patients and HbA1c itself is proportionately linked with excess Cardiovascular (CV) morbidity and mortality. Diabetes patients have increased at very high risk of coronary heart disease. These patients face an 11% increased risk of mortality from ischemic heart disease (UKPDS23) [14] while those with >8% HbA1c face 150% increased risk of death from heart disease [15] and this association is well established that NCEP III recommended treating diabetes with hyperlipidemia as if they already have previous CHD. Cardiovascular complications are usually present at diagnosis of T2DM. [16]

The present study was conducted to find out the association of oxidative stress produced by the hyperglycemia which was measured by Glycated hemoglobin and death during hospitalization in patients with ACS and to find out the effect of dyslipidemia in ACS patients. The study also finds out the prognostic significance of HbA1c level in hospitalized patients with ACS.

The study comprises of 98 ACS patients (men =72.4%) & (women =27.6%) who were admitted in Medicine Ward or ICCU). Study done by Houmond MK[17] has mentioned that CAD is most commonly seen in males compared to females, which also supports the present study. Classical risks factors like dyslipidemia, diabetes, hypertension, smoking were more common in men.

Majority of patients were in the age group of 51-65 years with mean age of 62.4 years (table 1). This finding is consistent with the previous reports which has been published on South Asian Population. [18] This may be due to the fact that the advance age is associated with lack of physical activity, environmental stress factors, unhealthy behaviors (alcohol and meat consumption), unemployment, all of which are contributing to an increased risk of developing CHD. [19]

In table 1 the prevalence of ACS patients was found more in rural region (54.1%) than urban region (45.9%). Majority of the patients admitted in RIMS hospital, Imphal are from rural areas. In other study similar findings were observed which may be due to fact that, in rural areas, smoking, tobacco consumption tends to since they are less literate, while it is declining in the more educated urban population. [20]

Figure 1, depicts that most of the ACS patients are smokers. This finding was also observed in other study.[21] Cigarette smoking is a traditional risk factor for ACS. Smoking act as a chronic promoter of atherosclerotic lesions and an acute risk factors increasing sympathetic stimulation and enhancing clotting.[22] Cigarette smoking increases oxidative damage by free radicals as indicated by increased product of lipid peroxidation and oxidation product of arachidonic acid[23] Exposure of LDL with smoking results in oxidation of lipid and greater uptake of modified LDL by macrophages which promote Atherosclerosis.

As seen in fig. 1 we found that 71% of the ACS patients are hypertensive and 28% are non-hypertensive. Similar finding were observed in study done by Olga M.[24] The increased incidence of AMI in hypertensive patients may be associated to several factors like endothelial damage, atherosclerosis, insulin resistance, left ventricular hypertrophy & ventricular arrhythmias. [25] Also the study group shows that most of the cases were diagnosed with STEMI (95%) also compared to NSTEMI which were only 5 % among the respondents.

In this study, all the ACS patients were divided into 3 groups depending on the level of HbA1c which is shown in table 2 as ADA guidelines.[13] HbA1c level less than 5.7% is considered as group 1(normal), HbA1c level 5.7-6.4% as group 2 (pre-diabetic) and greater than 6.5 % as group 3 (diabetic). Out of 98 patients, 13 patients had HbA1c value in normal range (< 5.7%) ,25 patients had value of HbA1c in the pre-diabetic range (5.7-6.4%) and 60 patients had value of HbA1c in the diabetic range (≥ 6.5%) . This finding were supported by a study done by Jain S et al. [21] Further the percentage of ACS patients having admission glucose level ≥200mg/dl was 63 patients as compared to 35 patients having admission glucose level <200mg/dl. This finding was also supported by Manal KAR et al on his study. Raised glucose is not only a symptom of glucose dysregulation, but also of stress and more high-risk patient population. Higher admission glucose is associated with a larger infarct size and a lower ventricular function. [26]. As seen in table 3, majority of the non-diabetes cases are in group 2 whereas among the diabetes cases most of the respondent are in group 3.

The study group shows that age, BMI, admission glucose, total cholesterol, LDL cholesterol, TG were increased with increased in HbA1c value (Table 4) except the mean value of serum HDL was decreased as the value of HbA1c increases and it was statistically significant (P value 0.004) which drive the pathways of inflammation, thrombosis & oxidation that leads to ACS.

In table 5, Serum HDL value was negatively correlated with HbA1c (-0.195) & p value (-0.053) which was not statistically significant. Admission glucose, total cholesterol and LDL are positively corelated significantly with HbA1c value. Manal KAR et al also supported the observation of our study. HbA1c is an easy marker of long-term glucose regulation, unmasking minor glucometabolic disease (impaired glucose tolerance, impaired fasting glucose or metabolic syndrome) [26]

In this study, the mortality of ACS patients were from Group 3, having HbA1c ≥ 6.5% irrespective of the diabetic status as compared to other group during hospitalization and it was statistically significant ($p < 0.011$) (table 6). This study found an association of elevated HbA1c, mortality rate (15%) after ACS and evaluated the prognostic significance of HbA1c in ACS patients with or without Diabetes. Similar results was found in the studies conducted by Malmberg et al pointed that there was an association between elevated HbA1c and mortality after myocardial infarction, at 30 days after discharge, when follow up all the cases were found to survive. This suggests that elevated HbA1c is not associated with 30 days mortality. [27]

In our study, maximum number of ACS patients were hospitalized for a minimum period of 8-14 days. Patients with ACS associated with diabetes had a longer stay in hospital (8-14 days) which results in increased management costs, as compared with non-diabetic ACS patients. When we observed the association of the cases who were hospitalized for about 8-14 days and HbA1c Groups, majority (62%) are found to be in HbA1c ≥ 6.5% group (3) which could be due to complication arises from oxidative stress due to elevated HbA1c.

5.CONCLUSION

This study shows that highest prevalence of ACS cases is in the age group 51-65 years and more in rural people. Males are affected more commonly and associated with smoking, diabetes and hypertensive respectively. It is also observed from this study that high admission blood glucose level is attributed by stress hyperglycemia. The reduction in serum total cholesterol does not prevent the risk of ACS but a decrease in serum HDL strongly predisposes to those individual at risk to an ACS.

The mortality of the ACS patients having HbA1c ≥ 6.5 during hospitalization was 15% and it was found to be statistically significant however it was not associated with thirty days mortality. The average period of hospital stay of all ACS patients is 8-14 days. The period of

hospital stay is longer in patient with diabetes as compared to non-diabetic ACS cases and higher HbA1c value, longer, is the hospital stay.

Consent :

A written informed consent was taken from all patients of this study.

Ethical :

Also, the project was granted by the institutional Ethics Approval Committee. After getting informed consent, a predesigned, pretested, semi structured interview was taken. A detailed history including the patients name, age, sex, presence of diabetes, hypertension, associated with smoking were also recorded.

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