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Research Article

Prognostic implications of glycated hemoglobin in nondiabetic patients with acute coronary syndrome

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ABSTRACT

Background: In nondiabetic patients with acute coronary syndrome, acute hyperglycemia is associated with adverse outcome. Whether this association is due merely to hyperglycemia as an acute stress response or whether longer-term glycometabolic derangements are also involved is uncertain. It was our aim to determine the association between chronic hyperglycemia (hemoglobin A1c (HbA1c) and outcome in nondiabetic patients with acute coronary syndrome.
Methods: This observational study included consecutive patients (n=47) without known diabetes mellitus admitted with acute coronary syndrome (STEMI, NSTEMI, UA). HbA1c was measured on admission. The main outcome was MACE (major adverse cardiac events including death, cardiogenic shock, arrhythmia, heart failure). The patients were divided into 2 groups according to their HbA1c level (group 1 HbA1c<5.7%, group 2 HbA1c>5.7%).
Results: There was no significant difference between baseline characteristics of both groups but complications were seen in higher number cases with HbA1c >5.7%. No significant difference in mortality was found. On multivariate logistic regression analysis HbA1c >5.7% was found to be an independent predictor of MACE.
Conclusions: There was no significant difference between baseline characteristics of both groups but complications were seen in higher number cases with HbA1c>5.7%. No significant difference in mortality was found. On multivariate logistic regression analysis HbA1c>5.7% was found to be an independent predictor of MACE.

Keywords: HbA1c, Acute coronary syndrome, Nondiabetic

INTRODUCTION

Coronary artery disease is the most important cause of death in industrialised countries and predicted to be the same in India by 2015.[1] Diabetes mellitus is one of the most important modifiable risk factors of coronary artery disease. It increases the risk of coronary artery disease by 2 to 4 fold.[2] Patients of myocardial infarction having diabetes mellitus have poorer prognosis than patients without diabetes mellitus.[3] The major pathobiologic attributor to this increased risk is hyperglycemia.[4] Though random blood sugar during a coronary event has been found to be a predictor of prognosis[5-7] but it cannot be accepted as an indicator of long term glycemic control as it is amenable to variation due to release of catecholamines as a stress response to the coronary event. On the other hand glycated haemoglobin is an established marker of long term glycemic control which can be used to evaluate the role of long term glycemic control on prognosis after acute coronary syndrome. But the prognostic importance of HbA1c in diabetic patients having acute coronary syndrome is still undefined.

Moreover, a recent report found that elevated HbA1c levels are also predictive for cardiovascular disease and mortality in patients without diabetes mellitus, indicating

that long term glycemic derangement in the subdiabteic range also increases cardiovascular risk.[8] Acute glycometabolic derangement in nondiabetic patients with myocardial infarction has already been proven to be a powerful predictor of prognosis[7]. However, until now, data on the predictive value of HbA1c levels, reflecting long-term glycometabolic control, in nondiabetic patients with myocardial infarction are limited. [9-11] The aim of the present study was to assess the prognostic impact of admission HbA1c in patients without known diabetes mellitus who were admitted with acute coronary syndrome.

METHODS

Patient characteristics

Consecutive patients admitted to our hospital for suspected ACS November 2012 to may 2014, were eligible in this prospective follow-up study. All hospitalized patients are screened for suspected ACS on the basis of admission diagnoses. The whole spectrum of ACS, including unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation MI (STEMI), was studied. The diagnosis of ACS was based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Patients with diabetes mellitus, chronic kidney disease, haemoglobinopathies and sepsis were excluded from the study.

Analysis of HbA1c on admission was done in every selected patient. The measurement of HbA1c was done by the National Glycohemoglobin Standardization Program–certified, DCCT standardised VARIANTTM II TURBO Haemoglobin testing system, Bio Rad laboratories by HPLC. Patients having HbA1c >6.5% were excluded from the study as they belonged to the diabetic category according to latest ADA guidelines.

Data collection

Data collection was done in a case record format. Demographic data and past medical history, including cardiovascular (CV) risk factors and comorbidities, were collected. The investigation results including blood tests and electrocardiographic findings were also recorded. All patients were followed up till discharge.

Endpoints

The composite primary endpoints of this study were the correlation of HbA1c level with major adverse cardiac events (MACE) during hospital stay. MACE included CV mortality, malignant arrhythmia, cardiogenic shock, congestive heart failure. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg or a drop of mean arterial pressure >30 mm Hg with a pulse >60 beats per minute to exclude shock secondary to bradycardia and/or low urine output (<0.5 mL/kg/h) with or without evidence of organ congestion.17 Malignant arrhythmia was defined as symptomatic sustained ventricular tachycardia and also ventricular fibrillation, irrespective of symptoms or hemodynamic stability.

Statistical analysis

We used SPSS version 20.0 (SPSS Inc., Chicago, IL) for statistical analysis. For the purpose of present analysis, patients were divided into 2 groups based on admission HbA1c: group 1, HbA1c ≥5.7% (the prediabetic group) and group 2, HbA1c< 5.7% (normal HbA1c group).

Continuous variables were presented as mean ± SD and categorical variables were presented as number of patients and percentage. Baseline characteristics of the 2 groups were compared using the $\chi 2$ test or the Fisher exact test for categorical variables and the Student unpaired t test for continuous variables, as appropriate. Association of various risk factors with MACE were analysed and significant variables were entered in a multivariate logistic regression analysis to determine independent predictability of risk factors. A Pearson coefficient of <0.05 was taken as significant.

RESULTS

The baseline patient characteristics are shown in the Table 1.

Except family history and HDL level there was no significant difference between the two groups.

Incidence of complications in both groups are shown in Table 2.

Complications like arrhythmia, cardiogenic shock and heart failure were seen in significantly higher number of patients with HbA1c >5.7%. There was significant difference in the mortality rates of both groups though all the 3 patients died had HbA1c>5.7%.

Association of risk factors with MACE is shown in Table 3.

Total cholesterol, LDL, HDL, HbA1c>5.7% are found to be the significant variables associated with MACE. The multivariate logistic regression analysis showed HbA1c>5.7% to be an independent predictor of MACE along with total cholesterol and LDL. The odds ratio was 1.991 with 95% Confidence interval from 1.091 to 2.116 and p value 0.021.

DISCUSSION

Our study shows that in ACS patients without known diabetes mellitus, incidence of MACE is higher in patients with higher HbA1c level i.e. long-term abnormalities in glucose control. Measurement of HbA1c

levels in nondiabetic patients may improve risk assessment in patients presenting with ACS.

Table 1: Baseline patient characteristics.

Base line characteristics	HbA1c<5.7% n=20	HbA1c≥5.7% n=27	P Value
Age in years (mean)	62.80±16.03	58.81±8.49	0.27
Sex (male : female)	12:98	13:14	0.57
H/O hypertension	5(25%)	12(44%)	0.17
H/O IHD	4(20%)	9(33%)	0.312
Family history	13(65%)	8(29%)	0.016
H/O smoking	12(60%)	10(37%)	0.114
H/O alcoholism	2(10%)	5(18.5%)	0.41
BMI (mean)	24.73±3.02	25.16±2.25	0.573
Mean BP at admission (mean)	91.80±15.69	89.11±13.94	0.539
Admission blood sugar (mean)	186.10±69.57	188.93±45.12	0.897
Total cholesterol (mean)	187.10±19.80	183.04±27.44	0.577
Triglyceride (mean)	172.95±41.73	163.63±29.20	0.372
LDL (mean)	81.35±12.65	98.67±43.70	0.093
HDL (mean)	40.20±7.32	32.56±5.54	<0.001
Haemoglobin (mean)	11.55±1.17	10.78±0.60	0.006
TLC (mean)	11015±3058	11211±1884	0.787
Diagnosis (STEMI:NSTEMI)	8:12	15:12	0.292
LV ejection fraction (mean)	54.15±3.93	55.00±4.59	0.50

Table 2: Incidence of complications in both groups.

Complication	HbA1c<5.7% n=20		HbA1c ≥5.7 n=27		P Value
	No.	%	No.	%	
Arrhythmia	0	0	8	29	0.008
Cardiogenic shock	2	10	10	36	0.03
Heart failure	3	15	13	49	0.01
Death	0	0	3	11	0.12

Although acute hyperglycemia on admission and during hospital stay has clearly been associated with adverse outcome in patients with acute myocardial infarction,[5-7] the prognostic value of admission HbA1c levels in this population has been less well established.

Table 3: Association of risk factors with MACE.

Base Line Characteristics	No Mace	Mace	P Value
Age in years (mean)	59.55	62.06	0.503
Sex (male : female)	12:17	9:9	0.563
H/O hypertension	41.3%	27.7%	0.345
H/O IHD	38%	11%	0.066
Family history	48%	38.8%	0.529
H/O smoking	44.8%	55.5%	0.479
H/O alcoholism	6.8%	11%	0.566
BMI (mean)	25.47	24.17	0.094
Mean BP at admission	92.72	86.28	0.143
Admission blood sugar	181.93	197.8	0.352
Total cholesterol (mean)	177.14	197.06	0.005
Triglyceride (mean)	161.48	177.44	0.130
LDL (mean)	76.90	114.50	<0.001
HDL (mean)	38.00	32.28	0.008
TLC (mean)	10613	11955	0.064
HbA1c >5.7%	44.8%	77.7%	0.026

Table 4: multivariate logistic regression analysis.

Risk factors	Odds ratio	95% Confidence interval		P Value
		Lower	Upper	
Total cholesterol	1.146	1.018	1.289	0.024
LDL	1.049	1.013	1.194	0.024
HDL	0.702	0.463	1.065	0.096
HbA1c>5.7%	1.991	1.091	2.116	0.021

HbA1c has been firmly established as an index of long term blood glucose concentration and as a measure of the risk for the development of major and minor complications in patients with diabetes mellitus.[12] Diabetes is diagnosed when the fasting plasma glucose level is consistently 7mmol/L or greater (≥126 mg/dl) or when the 2-hour plasma glucose level (after drinking a 75-g glucose load) is consistently 11.1 mmol/L or greater (≥200 mg/dl).[13] These levels were chosen because they effectively differentiated individuals at high risk for eye and kidney disease. They were not chosen on the basis of risk for cardiovascular disease. Thus, there is no a priori reason for this threshold to have any special significance with respect to the risk of cardiovascular disease.[14] This is also true for the glucose cut-off values for impaired glucose tolerance (2-hour post-glucose load value of 126-200mg/dl) which were not originally defined on the basis of identifying people at higher cardiovascular risk.[15] It is now clear that fasting and 2-hour glucose levels that are well below the diabetes cut-offs are cardiovascular risk factors. A progressive relationship between glucose and cardiovascular risk extends from normal glucose level right into diabetes range with no clear lower threshold.[14,15] Coutinho et al. carried out a meta-analysis of 20 studies for a total of 95,783 nondiabetic subjects and found an exponential relationship between the risk of

cardiovascular events and both fasting and postload plasma glucose levels. Such a relationship extended below diagnostic blood glucose levels for impaired fasting glucose or Impaired glucose Tolerance.[16] In the Norfolk cohort it was found that people with HbA1c>5% had greater cardiac risk than people with HbA1c<5% irrespective of their diabetic status.[17] Ko et al had shown that in nondiabetic individuals with normal glucose tolerance, HbA1c concentration correlated with higher age, blood pressure, total and LDL cholesterol, apolipoprotein B, urate concentration which are known cardiovascular risk factors.[18]

The above mentioned studies were regarding the increased risk of cardiovascular events with rise of HbA1c in nondiabetic patients whereas other studies have examined the prognostic importance of HbA1c in acute coronary syndrome. A large prospective study by Timmer et al found HbA1c to be an independent predictor of both short term and long term mortality.[19] Chowdhury et al had found similar results.[20] In a meta-analysis of 20 studies regarding prognostic importance of HbA1c in both diabetic and nondiabetic patients, Liu et al[21] found that HbA1c is an independent predictor of mortality in nondiabetic patients.

Several factors may play a role in the demonstrated association between HbA1c levels and adverse outcome. 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. 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.[22-25] Our findings indicate that these factors continue to play a negative role after cardiovascular disease has become clinically overt.

Because the number of patients with long-term abnormalities in glucose control and subsequent cardiovascular sequelae is likely to increase in the future decades, more tailored therapy should be investigated in this patient population. The European guidelines on diabetes mellitus, prediabetes, and cardiovascular disease recommend that people at high risk for type 2 diabetes mellitus should receive lifestyle counseling and, if needed, pharmacological therapy to reduce their risk of developing overt hyperglycemia and type 2 diabetes mellitus but especially to prevent or slow the development of cardiovascular disease.[26,27] This approach could also be encouraged in our patient population, and it may alter prognosis, although the benefits with regard to slowing the progression to diabetes mellitus still have to be elucidated.

Limitations of the study

The sample size of the study was small mostly due to unaffordability of patients. A larger sample size would have yielded better outlook towards the association of HbA1c with prognosis of patients with acute coronary syndrome. The follow-up period was short. A longer follow up would have allowed us to get more information regarding the prognostic implication of HbA1c in patients of acute coronary syndrome. Information regarding angiography could not be gathered. The information would have helped us to examine the association between HbA1c and number of vessel blocked. Patient who died within hours of presentation could not be included in our study.

CONCLUSIONS

HbA1c found to be an independent predictor of MACE following ACS in nondiabetic patients. Close follow-up of these patients seems warranted. More research is needed to better describe and understand these findings, and, more important, to assess and develop feasible treatment options.

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REFERENCES

1. K Park Coronary heart disease, Text book of preventive and social medicine,22 nd edition, M/S Banarasidas Bhanot, Jabalpur. 2005:339.
2. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetes in the Framingham population. Diabetes. 1974;23:105-16.
3. Wiviott, Stephen D. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis in Myocardial Infarction 38. Circulation. 2008;118,16:1626-36.
4. Orasanu, Gabriela, Plutzky J. The pathologic continuum of diabetic vascular disease. Journal of the American College of Cardiology. 2009:S35-S42.
5. Prakash D. Hyperglycemia and Acute Coronary Syndrome A Scientific Statement From the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2008;117.12:1610-19.
6. Selvin, Elizabeth. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. New England Journal of Medicine. 2010; 362.9:800-11.

7. Goyal A, Mehta SR, Diaz R, Gerstein HC, Afzal R, Xavier D. Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. Circulation. 2009;120:2429-37.
8. Timmer, Jorik R. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. American heart journal. 2004;148,3:399-404.
9. Stolar M. Glycemic control and complications in type 2 diabetes mellitus.Am J Med. 2010;123:S3–S11.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2010;33,(1):S62-S69.
11. World Health Organisation Study Group. Diabetes mellitus. WHO Tech Rep Ser. 1985;727:1-104.
12. Coutinho M, Wang Y, Gerstein HC, Yusuf S. The relationship between glucose and incident cardiovascular events. Diabetes Care. 1999;22(2):233-40.
13. Kay-Tee Khaw, Wareham N, Luben R, Bingham S, Oakes S, Wilch A. Glycated haemoglobin diabetes and mortality in men in North Cohort of European Prospective Investigation of cancer and nutrition (EPIL-NORFOLK). BMJ. 2001;322:15-32.
14. Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC. Glycated hemoglobin and cardiovascular risk factors in Chinese subjects with normal glucose tolerance. Diabetes Medicine. 1998;15:573-8.
15. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottevanger JP, Slingerland RJ. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation. 2011;124:704-11.
16. Grundy, Scott M. Pre-diabetes, metabolic syndrome, and cardiovascular risk. Journal of the American College of Cardiology. 2012;59,7:635-43.
17. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de BoerMJ. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28:88-136.

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