ORIGINAL STUDY

Predictive Value of Blood Glucose as an Independent Risk factor for Progression/ Mortality in Acute Coronary Syndrome.

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ABSTRACT
OBJECTIVES:
This study was designed to assess the prognostic significance of hyperglycemia in Acute Coronary Syndromes.
BACKGROUND:
Most studies that have examined this fact before were performed in patient with Acute Myocardial Infarction. [4, 18]

METHODS:
There were 320 patients admitted in M.U.III, Allied Hospital, Faisalabad between July2006 and December 2006. Patients were divided according to history of Diabetes Mellitus and further according to whether they had blood glucose more than 198 mg/dl. Other cardiac risk factors, medications and interventions were analyzed and multivariate logistic regression was used to determine the influence of blood glucose on progression/ Mortality. About 122 patients were lost in follow up
and 198 patients were followed for 2 months.

RESULTS:
In patients without history of diabetes, glucose levels were $\leq$ 198mg/dl in 136 patients (Group 1) and > 198 mg/dl in 24 patients (Group 2).

of those with diabetes glucose levels were $\leq$ 198 mg/dl in 11 patients (Group 3) and > 198 mg/dl in 27 patients (Group 4). Compare with Group 1 patients, the odds ratios (95% confidence interval) for in hospital progression/mortality among those in Group 2, 3 and 4 were 2.64 (1.32 to 4.52; p = .001), 1.63 (98 to 3.52; p = .035), and 1.88 (1.29 to 3.45; p = .012), respectively. These groups also have greater 2 months progression/mortality.

CONCLUSION:
Hyperglycemia in ACS is associated with worse prognosis in patients without diabetes. This finding signifies the underlying need for aggressive glucose management in these situations and perhaps more vigorous screening strategy for early recognition of diabetes. diagnosis of diabetes, was an independent predictor of in-hospital and 2 month morbidity and mortality. [9,24,36]

METHODS
Setting and Study Population: Allied Hospital, Punjab Medical College is a tertiary care hospital with 1500 beds and all state of the art modern facilities. Implications of elevated blood glucose were studies in 300 patient admitted to M.U. III during July,

INTRODUCTION
Diabetes Mellitus is now called a cardiovascular disease. [8,15,34] It is a major cardiovascular risk factor that has resulted in increase in prevalence of coronary artery disease[3,8,10].

Many cardiovascular risk factors are grouped in patients of diabetes mellitus and they are at increased risk of worse outcome during a period of unstability. [13,22] Patients with diabetes mellitus also have insulin resistance which is associated

with increased endothelial dysfunction and procoagulability state. [4,17]Patients either with or without a prior history of diabetes mellitus may present with hyperglycemia during ACS. [2,18,13] Among patients with no prior history of diabetes, hyper-glycemia may reflect previously undiagnosed diabetes, pre-existing glucose intolerance, stress-glucose intolerance, or a combination of these[1,6]. Several studies have reported an association between elevated blood glucose upon admission and subsequent increased adverse events, including CHF, cardiogenic shock, progression from Unstable Angina to Non ST elevation MI and from Non ST elevation MI to ST elevation MI and death. [11,31] However, an overview of these reports was critical of the varying definitions for hyperglycemia (blood sugars ranged from 119 mg/dl (6.6 mmol/l) to 200 mg/dl (11.1 mmol/l) and of the poor assessment of patient variables, previous medical therapy, and in-hospital interventions [5,33]. Many of these patient are admitted to general Medical wards and sometimes overlooked due to complete rely on conventional risk factors. [3,8,37] This study was designed to know whether hyperglycemia on admission, irrespective of the2006 to December, 2006. All patients admitted carrying the diagnosis of Acute Coronary Syndrome (ACS) were included and studied for during in hospital stay and for 2 Months of follow-up. Blood glucose test was carried out in all patients at admission and at discharge. All risk factors and medications were stratified and standardized. Patients were divided in 4 groups generally i.e. Group 1 without history of diabetes and blood glucose ≤ 198 mg/dl. Group 2 without history of diabetes but blood glucose more than 198 mg/dl. Group 3 with history of diabetes but blood glucose ≤ 198 mg/dl. Group 4 with history of diabetes and blood glucose more than 198mg/dl. All of these patients were closely studied during there stay at hospital. Patients with Unstable angina (USA) were lableled on conventional basis and those of Non ST elevation Myocardial infarction who have raised cardiac enzymes but without specific ECG changes for ST elevation MI. Patients who progressed from USA to NSTEMI and from NSTEMI to STMI or who died were considered as primary end point. There record was kept in specifically designed performas. All diagnosis types (including most responsible diagnosis, primary diagnosis, secondary diagnoses, and complications) were kept in record to ensure sensitivity.

DATE COLLECTION

All data was collected by authors and other specifically assigned doctors of our ward on specially made performas both during in hospital stay and during follow up visits in out patient department. Data pertaining to hospital admission, blood glucose on admission, admission medication, co morbid illness, treatment in hospital, discharge medication, results of investigations and out come were collected.

DATA QUALITY CONTROL

Quality control was achieved by rechecking and matching of data by different personals and standardization of terminology. Maximum efforts were made to maintain telephonic contact with patients and causalities were confirmed by charts and death certificates. Patients who were lost in follow up were not included in final assessment.

DATA ANALYSIS

Hyperglycemia was defined in study as a random blood glucose at admission that was >198 mg/dl as per the 2002 guidelines of the American Diabetic Association. Patients were stratified into four groups, based on their history of diabetes mellitus and the blood glucose level at admission:
Group 1: No previous history of diabetes and random blood sugar ≤198 mg/dl;
Group 2: No previous history of diabetes and random blood sugar >198 mg/dl;
Group 3: Known diabetes and random blood sugar ≤ 198 mg/dl;
Group 4: Known diabetes and random blood sugar >198 mg/dl.Study was an observational study and the data was collected as simple descriptive statistics. Chi square test was used to assess the difference in the distribution of categorical variables; t tests were used to compare the continuous variables. Multivariate analysis was done look for the independent predictors of in hospital and follow up progression and mortality. Variables those remained significant at p < .05 were included in final analysis. Strength of association of glycemic control was assessed by comparison of the three groups with disordered blood glucose profile
(Group 2,3 & 4) to normal (Group 1) patients without previous diagnosis of diabetes and random blood glucose ≤ 198mg/dl.

RESULTS

198 patients were admitted and followed for 2 months in Medical Unit-III. 141(71.21 %) patients were admitted with diagnosis of USA and 57 (28.79%) with diagnosis of NSTEMI. In hospital progression/mortality rate was 14.8% for patients with USA and 13.9% for patients with NSTEMI. Cumulative progression/mortality was 19.6% for USA and 16.5% for NSTEMI, respectively.

80.8% of study population did not have history of diabetes. The normal (reference) cohort made 68.9% of the study population. Patients who were not diabetic but were hyperglycemic at time of admission were 12.1 % of the study population. Patients with known diabetes and normal blood glucose on admission were5.5% of total while patients who were diabetic and had blood glucose levels more than 198mg/dl were 13.6% of total study population.

Characteristics of patient divided in four groups are given below

Table I
Patient Characteristics According to Diagnosis of Diabetes and Glycemic Status

Variable	Group 1[*] (n = 136)	Group 2[†] (n = 24)	Group 3[‡] (n = 11)	Group 4[§] (n = 27)	p Value
Age (yrs)	57.6	62.8	61.5	61.1	< 0.0001
Male (%)	63.4	50.1	63.6	57.6	< 0.0001
Glucose (mg/dl)	130	326	158	316	< 0.0001
Creatinine (mg/dl)	1.06	1.13	1.09	1.03	< 0.0001
Smoker (%)	68.8	51.3	65.3	53.9	0.0112
Hypertension (%)	39.4	46.5	64.6	62.9	< 0.0001
Hyperlipidemia (%)	26.9	18.2	36.1	40.9	0.0013
Prior-myocardial infarction (%)	12.8	26.3	31.6	36.9	0.0028
Prior heart failure (%)	4.6	19.6	16.8	26.2	< 0.0001
PVD (%)	2.6	1.9	3.4	8.9	0.0647

Group 1 = No previous diagnosis of diabetes and mg/dl (11 mmol/l).
[†] Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl.
[‡] Group 3 = Known diabetes and random blood glucose ≤198 mg/dl.

[§] Group 4 = Known diabetes and random blood glucose >198 mg/dl.

Patients known to have diabetes were significantly older than "normals," yet the oldest group of patients had hyperglycemia but no known history of diabetes. Males made up almost 63% of the normal-glucose non-diabetic group, but only half of the non-diabetic hyperglycemic group. Other major cardiac risk factors had a variable distribution. Patient group with known diabetes was having greater likelihood of having previous myocardial infarction irrespective of the glucose level.

Admission medication are given below in the table. In general patients with diabetes were more likely to have received intensive cardiovascular therapy with all available options including aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and hydroxymethylglutaryl-coenzyme A reductase inhibitors. Conversely patients having hyperglycemia but not diabetes did receive less aggressive cardiovascular therapy on presentation.

Table II
Admission Medication According to Diagnosis of Diabetes and Glycemic Status

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMG CoA = hydroxymethylglutaryl-coenzyme A reductase inhibitor.
[*] Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/L).
[†] Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl.
[‡] Group 3 = Known diabetes and random blood glucose ≤198 mg/dl.
[§] Group 4 = Known diabetes and random blood glucose >198 mg/dl.

Multivariate analysis identified several variables that were independently associated with in-hospital mortality. Diabetic status, irrespective of glucose level upon admission, was a predictor of adverse outcome; but patients with hyperglycemia and no history of diabetes had an even worse outcome, with more than a twofold higher risk. Patients known to have diabetes and those with hyperglycemia without a history of diabetes continued to suffer a relatively worse outcome even up to one year. Variables associated with lower in-hospital mortality include exposure to disease-

modifying drugs known to be associated with long-term benefit.

Table IV
Independent Predictors of Outcome

Variable	Odds Ratio	95% CI	p Value
Group 1[*]	1.00	---	---
Group 2[†]	2.64	1.32-4.52	0.001
Group 3[‡]	1.63	.98-3.52	0.035
Group 4[§]	1.88	1.29-3.45	0.012
Peripheral vascular disease	4.33	1.88-9.96	0.0006
Insulin on admission	2.05	1.07-3.92	0.0299
Prior heart failure	1.81	1.09-3.00	0.0219
Prior myocardial infarction	1.95	1.28-2.98	0.0020
Female	1.66	1.31-2.43	0.0096
Aspirin on admission	0.53	0.33-0.86	0.0101
ACEI on admission	0.46	0.26-0.79	0.0052
Beta blocker on admission	0.25	0.14-0.44	< 0.0001
Digoxin on admission	0.13	0.04-0.47	0.0018
HMG CoA on admission	0.06	.01-0.46	0.0067

ACEI = Angiotensin-converting enzyme inhibitor; CI = confidence interval; HMG CoA = hydroxymethylglutaryl-coenzyme A reductase inhibitor.

[*] Group 1 = No previous diagnosis of diabetes and random blood glucose ≤198 mg/dl (11 mmol/l).

[†] Group 2 = No previous diagnosis of diabetes and random blood glucose >198 mg/dl.

[‡] Group 3 = Known diabetes and random blood glucose ≤198 mg/dl.

[§] Group 4 = Known diabetes and random blood glucose >198 mg/dl.

DISCUSSION

It is evident from the study that patients presenting with ACS who are hyperglycemic on admission represent a high-risk population. The worst outcomes occurred among those without a prior history of diabetes. This may relate to hyperglycemia being associated with several high-risk features, including older age, female gender, and a prior history of heart failure. However, an elevated blood sugar upon admission was correlated with more in-hospital heart failure and greater in-hospital and one-year mortality independent of a history of diabetes mellitus or of any of the high-risk features listed earlier. Furthermore, hyperglycemia conferred risk independent of body mass index or history of

Admission Medication	Group 1 (n=136)	Group 2[†] (n=24)	Group 3[‡] (n=11)	Group 4 (n= 27)	< 0.0001
Oral hypoglycemic (%)	0	0	50.3	62.8	<0.0001
Insulin (%)	0	0	20.7	27.7	<0.0001
Aspirin (%)	31.1	25.2	33.1	35.1	0.2128
ACEI (%)	18.9	23.0	30.8	34.8	<0.0001
ARB (%)	1.9	0	2.4	4.6	0.0145
Beta-blocker (%)	31.1	25.2	41.4	37.2	0.0042
CCB (%)	5.1	10.4	14.8	9.9	<0.0001
HMG	15.1	5.5	17.8	16.0	<0.0001
Nitrates (%)	21.6	26.7	30.2	34.8	<0.0001
Digoxin (%)	3.4	6.7	7.1	7.1	0.0126

hyperlipidemia, suggesting that glucose status itself may be contributing to, or is a key marker of, adverse outcome.

STRESS HYPERGLYCEMIA

In literature it is unclear that whether stress hyperglycemia directly predisposes patient to worse prognosis or it is just a marker of poor outcome. [30, 38]Although it is not clear but studies suggest that an elevated blood glucose level, whether acute or chronic, adversely affects endothelium-dependent vasodilation and impairs macrophage and lymphocyte function. [12,16,21]Hyperglycemia during ACS may reflect a compromised metabolic state and is associated with a surge of serum catecholamines and decreased insulin sensitivity. [19,26,32]

If stress hyperglycemia indeed reflects an underlying dysglycemic state, then this would be expected to correlate with a higher overall risk for more extensive coronary artery disease and would explain a worse prognosis after ACS.[20,35] Elevated blood glucose reflects both acute stress and predict an increased propensity for long term cardiovascular events. [23,25,29]

HYPERGLYCEMIA AND UNRECOGNIZED DIABETES MELLITUS

Hyperglycemia in non-diabetic patients most likely represents undiagnosed diabetes. 12.1 % of population in this study which have hyperglycemia but no prior history of diabetes mellitus mostly represent this fact. [14,20,27] This percentage is greater than

international values showing lack of public health awareness and lack of adequate fasclities.

Many of these patients had proved to be diabetics or having impaired glucose tolereance in follow up but this was not an universal finding. In this study this population had worse prognosis even than patients with know diabetes and hyperglycemia. This probably can be explained by that these patients were actually diabetic for many years but did not received any treatment which could confer a protective benefit. In comparison diabetics although not controlled at time of admission but were receiving some kind of treatment which decreased the morbidity and mortality.

STUDY LIMITATIONS

This was an observational study and it was not randomized. The true incidence of population presenting with Ischemic heart Disease and have first time recognized hyperglycemia cannot be established by this small study.

CONCLUSIONS

Hyperglycemia at time of admission in patients with ACS irrespective whether they are diabetic or not is associated with worse out come at least in a subgroup of patients. These patients are older have multiple cardiac risk factors, and are more likely to have a prior history of heart failure. These patients are at high risk of progression of disease in hospital and after discharge and at 2 month of follow up even with intensive therapy.

It is probably suggested that all population should have a screening program to detect this population and early intervention with lifestyle modification and medical treatment can decrease morbidity and mortality. It is also evident that patient who have raised blood glucose level at admission need more extensive and aggressive strategies.

REFERENCES:

1. Fava S, Aquilana O, Azzopardi J, Agius Muscat H, Fenech FF. The prognostic value of blood glucose in diabetic patients with acute myocardial infarction. Diabet Med. 1996;13:80–83
2. Banarjee AK. Blood sugar and prognosis of myocardial infarction in the elderly. Br J Clin Pract. 1986;40:516–517
3. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non–Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000;102:1014–1019
4. Lynch M, Gammage MD, Lamb P, Nattrass M, Pentecost BL. Acute myocardial infarction in diabetic patients in the thrombolytic era. Diabet Med. 1994;11:162–165.
5. Husband DJ, Alberti KG, Julian DG. "Stress" hyperglycaemia during acute myocardial infarction: an indicator of pre-existing diabetes? Lancet. 1983;2:179–181
6. Bolk J, van der Ploeg T, Cornel JH, Arnold AE, Sepers J, Umans VA. Impaired glucose metabolism predicts mortality after myocardial infarction. Int J Cardiol. 2001;79:207–214
7. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol. 2000;36:959–969.
8. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2002;25:S1–147
9. Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. J Am Coll Cardiol. 2000;36:355–365
10. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;356:773–778.
11. Norhammer AM, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. Diabetes Care. 1999;22:1827–1831.
12. Malmberg K, Norhammer A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction. Circulation. 1999;99:2626–2632.
13. O'Sullivan JJ, Conroy RM, Robinson K, Hickey N, Mulcahy R. In-hospital prognosis of patients with fasting hyperglycemia after first myocardial infarction. Diabetes Care. 1991;14:58–60

14. Oswald GA, Corcoran S, Yudkin JS. Prevalence and risks of hyperglycemia and undiagnosed diabetes in patients with acute myocardial infarction. Lancet. 1984;:1264–1267

15. Ravid M, Berkowicz M, Sohar E. Hyperglycemia during acute myocardial infarction: a six year follow-up study. JAMA. 1975;233:807–809

16. Bellodi G, Manicardi V, Malavasi V, et al. Hyperglycemia and prognosis of acute myocardial infarction in patients without diabetes mellitus. Am J Cardiol. 1989;64:885–888

17. SPRINT Study GroupLeor J, Goldbourt U, Reicher-Reiss H, Kaplinski E, Behar S. Cardiogenic shock complicating acute myocardial infarction in patients without heart failure on admission: incidence, risk factors, and outcome. Am J Med. 1993;94:265–273.

18. Oswald GA, Smith CCT, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction. Br J Med. 1986;293:917–922

19. Herlitz J, Bang A, Karlson BW. Mortality, place and mode of death and reinfarction during a period of 5 years after acute myocardial infarction in diabetic and non-diabetic patients. Cardiology. 1996;87:423–428

20. Gwilt DJ, Petri M, Lamb P, Nattrass M, Pentecost BL. Effect of intravenous insulin infusion on mortality among diabetic patients after myocardial infarction. Br Heart J. 1984;51:626–630

21. Soler NG, Frank S. Value of glycosylated hemoglobin measurements after acute myocardial infarction. JAMA. 1981;246:1690–1693

22. Sewardsen M, Vythilingum S, Jialal I, Becker PJ. Prognostic importance of admission plasma glucose in diabetic and non-diabetic patients with acute myocardial infarction. Q J Med. 1989;265:461–466

23. ICONS InvestigatorsCox JL. Optimizing disease management at a health care system level: the rationale and methods of the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) study. Can J Cardiol. 1999;15:787–796

24. Meltzer S, Leiter L, Daneman D, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ. 1998;159:S1–30

25. Tenerz A, Lonnberg I, Berne C, Nilsson G, Leppert J. Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? Eur Heart J. 2001;22:1102–1110

26. Rytter L, Troelsen S, Beck-Nielsen H. Prevalence and mortality of acute myocardial infarction in patients with diabetes. Diabetes Care. 1985;8:230–234

27. Aronson D, Rayfield EJ, Chesebro JH. Mechanisms of determining course and outcome of diabetic patients who have had acute myocardial infarction. Ann Intern Med. 1997;126:296–306

28. Haffner SM. The importance of hyperglycemia in the nonfasting state to the development of cardiovascular disease. Endocr Revs. 1998;19:583–592

29. Tansey MJ, Opie LH. Plasma glucose on admission to hospital as a metabolic index of the severity of acute myocardial infarction. Can J Cardiol. 1986;2:326–331

30. Williams SB, Goldfine AB, Timimi FK, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. Circulation. 1998;97:1695–1701.

31. Kreisberg RA. Diabetic dyslipidemia. Am J Cardiol. 1998;82(Suppl):67U–73U.

32. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin dependent diabetes mellitus. J Am Coll Cardiol. 1996;27:567–574.

33. Holubarsch C, Ruf T, Goldstein DJ, et al. Existence of the Frank-Starling mechanism in the failing human heart: investigations on the organ, tissue, and sarcomere levels. Circulation. 1996;94:683–689.

34. Marcus JT, Gotte MJ, Van Rossum AC, et al. Myocardial function in infarcted and remote regions early after infarction in man: assessment by magnetic resonance tagging and strain analysis. Magn Reson Med. 1997;38:803–810.

35. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22:233–240

36. Yudkin JS, Oswald GA. Determinant of hospital admission and case fatality in diabetic patients

with myocardial infarction. Diabetes Care. 1988;11:351–358.

37. Chowdhury TA, Lasker SS. Elevated glycated haemoglobin in non-diabetic patients is associated with an increased mortality in myocardial infarction. Postgrad Med J. 1998;74:480–481

38. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infraction in patients with diabetes mellitus. Br Med J. 1997;314:1512–1515

EDITORIAL COMMENTS

Patients who present with ACS and are hyperglycemia upon admission, represent a high risk population. This is an observational study of prognostic significance. The objective is well set and the sample of patients is adequate.

Statistical analysis of the data has been done by using applicable tests, and the results are adequately interpreted.

There is good utilization of tables at various stages, with proper grouping of patients. References have been quoted correctly, with use of some recent references as well.

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