IN-HOSPITAL MORTALITY IN ACUTE CORONARY SYNDROME PATIENTS WITH AND WITHOUT ADMISSION HYPERGLYCAEMIA: A COMPARATIVE STUDY

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ABSTRACT

Background: Admission hyperglycaemia, which has been regarded as stress induced, is very common and poses an adverse effect in the outcome and in-hospital mortality of ACS patients. We evaluated the association of admission blood glucose with the in-hospital mo¥fatality of unselected patients with acute coronary syndrome (ACS).

Methods: 88 patients of ACS with or without admission hyperglycaemia were enrolled. Patients were stratified according to their admission blood glucose levels into two groups: with admission hyperglycaemia: >/= 140 mg/dl (n=44, 50%) and without admission hyperglycaemia: </= 140 mg/dl (n=44, 50%). Patients with ACS were first compared against with and without hyperglycaemia. Then they were subdivided into STEMI/NSTEMI/UA and the data were analyzed again.

Results: The mean age of the patients was 63.81 (SD 12.34) and male were 43 (48.9%). The overall mortality in the population was (29 out of 88 ACS patients) 32.9%. Male were more likely to present with admission hyperglycaemia (Male Vs. Female 31 Vs. 13) (p<0.001). Patients with admission hypertension were more likely to present with admission hyperglycaemia (Hyperglycaemia Vs. Normoglycaemia 66.6% Vs. 33.3%) (p<0.003). KILLIP class I patients had higher chances of presenting with admission normoglycemia (Hyperglycaemia Vs. normoglycemia 19 Vs. 28) (p=0.054) whrereas those having previous diabetes mellitus were more often presenting with admission hjyperglycaemia (hyperglycaemia Vs. normoglycemia 22 Vs 3) (p<0.01). Patients without admission hyperglycemia were more likely to be discharged than those with admission hyperglycaemia (hyperglycaemia Vs. normoglycemia 20 Vs. 30) (p=0.031). The in-hospital mortality in admission hyperglycaemia group was 19 (65.5%) whereas that without admission hyperglycaemia was 10 (22.7%). Hence, patients with admission hyperglycaemia were more likely to have more in-hospital mortality as compared to those who do not have admission hyperglycaemia (<0.041). STEMI with admission hyperglycaemia were more often male (hyperglycaemia Vs. normoglycaemia 70% Vs. 30%) (p=0.001), more likely to receive insulin at ER (hyperglycemia Vs. Normoglycaemia 46.7% Vs 16.7%) (p=0.012). NSTEMI patients with admission hyperglycaemia were more likely to receive insulin in ER (p<0.007) and UA with admission hyperglycaemia had longer hospital stay compared to admission normoglycemia (hyperglycaemia Vs. normoglycemia 8.5 days Vs. 3.33 days) (p<0.001).

Conclusion: This study indicates that admission hyperglycaemia is common in acute coronary syndrome patients and is a powerful predictor of increased in-hospital mortality in such patients.

KEYWORDS: *acute coronary syndrome, admission hyperglycaemia, in-hospital mortality,*

1. INTRODUCTION

Acute coronary Syndrome is composed of patients with acute myocardial infarction (AMI) with ST-segment elevation on their presenting electrocardiogram (ECG) (STEMI) and those with unstable angina (UA) and non ST-segment elevation MI (UA/NSTEMI).

UA is defined as angina pectoris or equivalent ischemic discomfort with at least one of three features: (1) it occurs at rest (or with minimal exertion), usually lasting > 10 minutes; (2) it is severe and of new onset (i.e., within the prior 4-6 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously).

The diagnosis or NSTEMI is established if a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers.

The clinical hallmark of UA/NSTEMI is chest pain, typically located in the substernal region or sometimes in the epigastrium that radiates to the neck, left shoulder, and/or the left arm. This discomfort is usually severe enough to be described as frank pain. Anginal "equivalents" such as dyspnea and epigastric discomfort may also occur, and these appear to be more frequent in women.

If the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; tachycardia; a third and/or fourth heart sound; basilar rales; and, sometimes, hypotension, resembling the findings of large STEMI.[1]

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis.

Slowly developing, high-grade coronary artery stenosis do not typically precipitate STEMI because of the development of a rich collateral network over time. Patients that are at increased risk for developing STEMI include those with multiple coronary risk factors and those with unstable angina.

Chest pain that is heavy, squeezing, and crushing, and sometimes stabbing or burning is the most common presenting complaint in patients with STEMI. It commonly occurs at rest, is usually more severe, and lasts longer and typically involving the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiate include the abdomen, back, lower jaw, and neck. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom.[2]

An epidemic of coronary heart disease (CHD) began during the 20th century in most industrialized countries, where CHD was a leading cause of mortality among adults. Here, although there is an increase in the overall prevalence of IHD, there has been a decline in the IHD related age-adjusted death rates primarily due to an increased awareness, heart healthy life-styles and better pharmacological interventions. Moreover, improved medical, interventional and surgical options are readily available for ACS and chronic IHD patients contributing to the better outcome in ACS patients.[3] Presently, developing countries show the beginnings of the same epidemic that the developed nations were facing previously.[4] There has been a marked increase in the burden of IHD in developing countries and an increasing trend in the age-adjusted death rates, with are primarily due to the social and economic changes that have occurred main cardiovascular risk factors.[3] Reliable information on population incidence, prevalence, and case-fatality rates of CHD is essential to understanding, treating, and controlling the but in developing countries it is generally unavailable.[5]

Unstable angina and non-ST segment elevation myocardial infarction account for about 2.5 million hospital admissions worldwide and are a major cause of mortality and morbidity and morbidity in Western countries.[6] ACS is not only a common cause of medical consultations and admissions at emergency departments, but also is a major cause of morbidity and mortalit.[7] Although a definite consensus on death due to ACS is unavailable for the

developing countries, cardiovascular diseases are increasing in an overwhelming fashion in this region. Between 1990 and 2020, the disease is estimated to increase by 137% in men and 120% in women in these countries, compared to 30-60% increase in the developed countries.[8] Furthermore, south Asians have a high prevalence of risk factors and they have earlier age of inset and more people suffer from SREMI.[9] Even, South Asian migrants living in several countries have higher death rates from coronary heart disease (CHD) at younger ages compared with the local population despite apparently lower levels of conventional risk factors.[8] [10]-[13] Cardiovascular deaths also occur 5 to 10 years earlier in South Asian countries then they do in Western countries.[14][15] This has raised the possibility that South Asians exhibit a special susceptibility for acute myocardial infarction (AMI) that is not explained by traditional risk factors.[9]

Admissions hyperglycaemia is common in patients with ACS and is regarded as stress induced which leads to various catecholamine release and sympathetic activation during the episode stimulating gluconeogenesis, glycogenolysis and lipplysis.[16][17] The Euro Heart Survey on Diabetes and the Heart analyzed the prevalence (ACS). Among patients with no previous history of diabetes, impaired fasting glucose (IFG), impaired glucose tolerance or new onset hyperglycaemia (NH) was found in 58% of patients.[16]

Hyperglycaemia on admission is a powerful predictor of survival and increased risk of in- hospital complications in patients both with and without diabetes mellitus. Despite the findings from prior studies, many gaps in knowledge currently exist in our understanding of the association between elevated glucose levels and adverse outcomes in patients with ACS.[18]

As already stated, may the patient be a diabetic or a non-diabetic, admission glycaemia poses an increased risk of mortality[19] and the treatment of admission hyperglycaemia in the emergency ward can be beneficial for their suevival.[20] Admission hyperglycaemia is even a stronger predictor for mortality in patients without a medical history of diabetes.[21]

A recent analysis of the Cooperative Cardiovascular Project (CCP) which included a large cohort of patients (n=141680) with ACS showed that depending on different levels of glucose on admission ($\leq$ 110, 110 to 140, 140 to 170, 170 to 240 and $\geq$240 mg/dl), new hyperglycaemia was associated with a significant 13% to 77% relative increase in short-term mortality and a 7% to 46% relative increase in 1-year mortality.[16] The overall in-hospital mortality is approximately 15%.[22]

1.1 Causes of acute hyperglycaemia and increased mortality in ACS:

Principally, three main hypotheses have been postulated as to why hyperglycaemia may cause increased mortality in acutely ill patients: (overview shown in Fig.)

1. Elevated blood glucose can be a physiologic response to hormones, such as epinephrine or cortisol, which are released under high systemic stress and, therefore, may indicate greater overall illness severity.[23] For example, patients with larger areas of myocardial ischemia and more impaired left ventricular function may have higher sympathetic activation leading to higher glucose levels.

2. Hyperglycaemia may be an indicator of systemic and organ-specific metabolic dysregulation, especially impaired insulin signaling. Insulin resistance not only cause hyperglycaemia but may also cause a reduction in energy production in the heart, producing a lower tolerance to hypoperfusion. Because the downstream

molecules in the insulin signaling cascade have well-established cytoprotective effects, reduced insulin signaling may increase the likelihood of ischemic injury due to the loss of cytoprotective effect when insulin-signaling pathways are disrupted.[24][25]

3. Acute hyperglycaemia activates other pathologic processes that could cause cellular and tissue injury, such as increasing free radial formation and oxidative stress, induction of a prothrombotic state, and worsening endothelial function.[26]-[29]

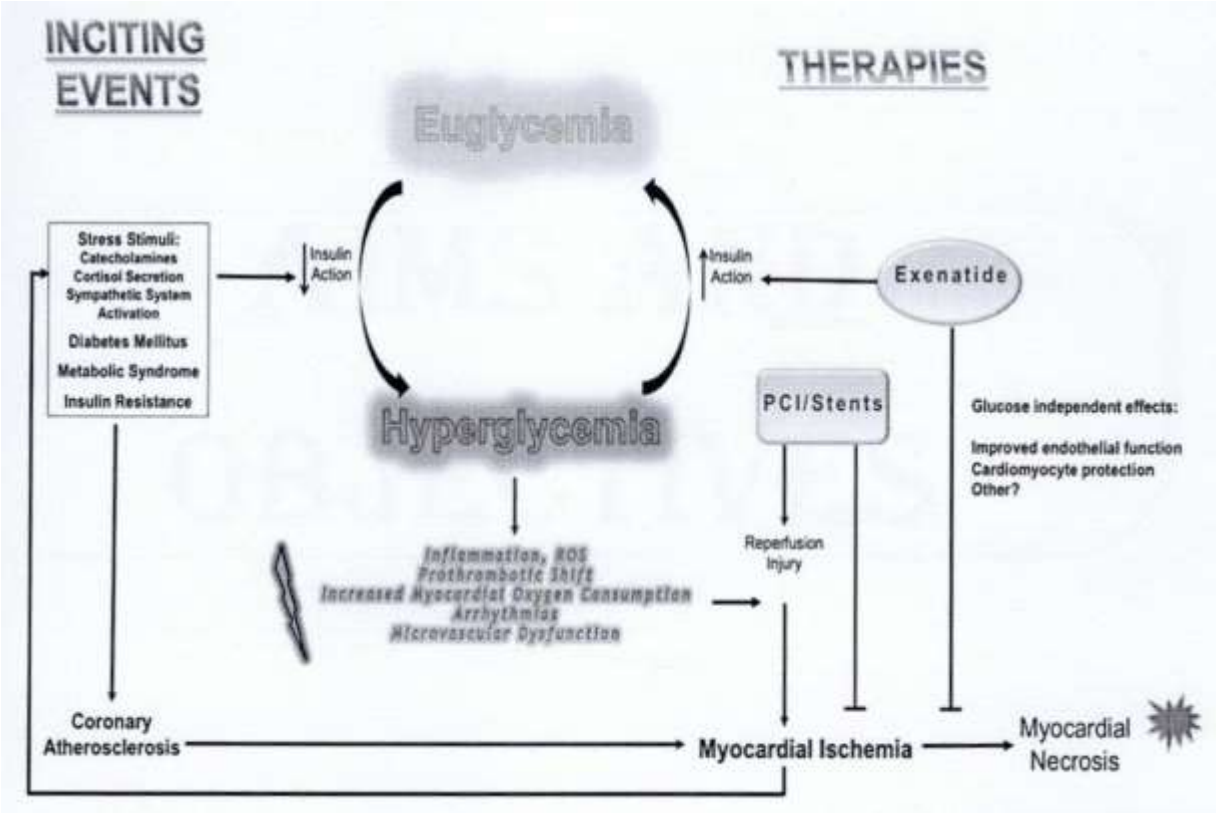

Fig: Summary of hypothetical relatical relationship(s) between hyperglycaemia and adverse outcomes in patients with ACS and posited mechanisms of the beneficial effects of exenitide and PCI/stents.[30]

1.2 Methods

All Patients of age more than 18 years presenting to the Emergency ward of BPKIHS with Acute Coronary Syndrome were included. The patients were followed up after admission from the emergency ward through the ICU/CCU to the medical wards. Patient's history, including various clinic-epidemiological data, investigation report and final outcome were noted. The spectrum of diagnosis covered acute coronary syndrome, defined by characteristic symptoms and/or ECG changes and enzymes (total creatine kinase (CK total) or creatine kinase MB fraction greater than twice the upper limit of normal), minimal necrosis (the same, but the enzymes below twice the upper limit of normal and troponin-positive) and unstable angina (symptoms and/or ECG typical for ACS, normal enzymes). Patients were defined as diabetic when diabetes mellitus was reported in the past medical history; independent of the kind of treatment they were receiving (oral agents, insulin-treated of untreated). other risk factors previously diagnosed, treated and/or documented in the patients' medical history were identified. Patients

were stratified into two admission glycaemia groups: Normal (admission blood glucose level </= 140 mg/dl) and Hyperglycaemia (Admission blood glucose level > 140 mg/dl).Within these two groups, types of ACS (STEMI/NSTEMI/UA), short-term outcome of diabetic versus non-diabetic patients, relevance of using insulin in the emergency ward for hyperglycaemia and in- hospital mortality were compared.

Blood glucose, CK MB, CK Total and Troponin I were measured from the venous Blood glucose, CK MB, CK Tatal and Troponin I were measured from the venous blood sample drawn during the admission of the patients to the emergency Ward. Such blood was centrifuged and the serum is analyzed. Troponin I was analyzed by Trop I Kit (ACON) while random blood sugar and CK MB and CK total were analysed in Accent 200 (Cormay). However, quantitave estimation of Troponin 1 was not performed.

1.3 Statistical Analysis

Data are presented as percentages of discrete variables and as mean (SD) and/or medians with interquartile range for continuous variables. Differences in baseline characteristics were compared using the chi-squared test. A p value <0.05 was considered statistically significant. IBM SPSS statistics 11.5 was used for all statistical analyses.

2. RESULTS

2.1 Overall patient population of ACS

Total of 88 acute coronary syndrome (ACS) patients were included in the stady. Of the 88 cases, 44 patients had admission Normoglycaemia (blood sugar level </=140mg/dl) and 44 patients had admission hyperglycaemia (blood sugar level >140mg/dl). Total female patients were 45 (51.1%) and male patients were 43 (48.9%). Male patients were more likely to present with admission blood sugar level >/=140~mg/dl than the female patients (70.5% Vs. 29.5%) whereas female patients were more likely to present with admission blood sugar level < 140 mg/dl than males (72.7% Vs 27.3%). Patients known to have diabetes were 25 (28.4%) and 63 (71.6%) patients were non-diabetic or their diabetes status was not known

The mean age of presentation for the patients who had admission normoglycaemia was 64.98 years whereas that in the group with admission hyperglycaemia was 62.84 years. ACS patients with age less than 50 yrs were 13 (14.8%), >/=50 to <60 years were 18(20.5%), >/=60 to <70 years were 25(28,4\%) and that of >/=70 were 32(36,4\%). Hence, it was seen that ACS Incidence increases as the age of the patient advances. Forty six patients presented with admission blood pressure <140/90 mmHg while 42 presented with admission blood pressure >/=140/90 mmHg.

		Hyperglyceamia	Normoglycaemia	P Value
Outcome	discharged(%)	20(45.4)	30(68.2)	0.031
	LAMA/DOPR/ Referred(%)	5(11.4)	4(9.1)	0.725
	Expired (%)	19(43.2)	10(22.7)	0.041
In-hospital mortality(%)		19(65.5)	10(34.4)	0.041
Age (yrs)	Min-Max	33-82	40-90	
	Mean(SD)	62.84(11.41)	64.98(13.23)	
	Median	64	61.5	0.507
Admission Blood Glucose(mg/dl)	Min Max	143-481	56-140	
	Mean(SD)	237.77(83.68)	64.98(19.99)	
	Median	212	112.5	
Admission Systolic BP (mmHg)	Min Max	unrecordable-200	unrecordable-170	
	Mean(SD)	121.55(45.54)	120.77(40.84)	
	Median	140	120	0.003
Admission diastolic BP (mmHg)	Min Max	unrecordable-140	Unrecordable-100	
	Mean(SD)	79.45(30.163)	71.59(21.88)	
	Median	83	80	0.016
Pack year	Min Max	0-25	0-30	
	Mean(SD)	3.95(7.48)	4.66(8.18)	
	Median	0	0	0.453
CK MB (Units)	Min Max	0-398	0-362	
	Mean(SD)	107.05(105.12)	87.50(93.81)	
	Median	64	42	0.267
CK Total (Units)	Min Max	0-3840	0-5577	
	Mean(SD)	755(848.32)	958(1261.47)	
	Median	372	363.5	0.881
Hospital stay (days)	Min Max	1-15	1-13	
	Mean(SD)	5.14(3.68)	5.30(3.40)	
	Median	5.5	6	0.641

Table 1: Overall patient population of ACS

Four (84.1%) ACS patients presented with left sided chest pain, 12 (13.6%) presented with epigastric pain, 32(36.4%) with shortness of breath and 13 (14.8%) patients had nausea and vomiting during presentation. Seven

(8%) patients were under medication with aspirin previously, 10(11.4%) with past ACE Inhibitors/AT-I antagonists, 4(4.5\%) were on past nitrates, 6(6.8%) on past Beta-Blockers and 23 (26.1%) on past calcium channel blockers (CCBs). Current smokers were 32 (36.4%) while non-smokers were 56 (63.6%). Among the smokers, who smoked

</=20 pack year were 25(28.4\%) and those who smoked more than 20 pack year were 7 (8%). The mean pack year in group with admission Normoglycemia was 4.66 while that in the group with admision hyperglycemia was 3.95. Troponin I was found to be positive in 69 (78.4%) cases

Twelve (13.6%) ACS patients had normal ECG. ST Elevation in the ECG was seen in 48(54.5%). T wave inversion in 18 (20.5%) and both ST Elevation with T inversion was seen in 10(11.4%) patients. KILLIP class I was seen in 47 (53.4%). KILLIP II in 21(23.9%) and KILLIP III/IV in 20(22.7%) patients. History of hypertension in the past was present in 37(42.5%) patients while only 9(10.2%) bad dyslipidemia in the past. Ant wall STEMI was noted in 15 (17%) patients, 14(15.9%) patients had antero-septal STEMI, 6(6.8%) patients had antero- lateral STEMI and 20(22.7%) had Inferior wall STEMI. Antero-inferior wall STEMI was seen in 1 (1.19%) patient, septal and lateral wall STEMI in 1(1.1%) patient and inferior wall with RV infarction in 3(3.4%) patients. NSTEMI was seen in 21(23%) patients while Unstable Angina was present in 7(7.9%) patients. Thirty six (40.9%) patients were treated with PCI along with medical management whereas 52(59.1%) patients were treated with medical management alone. Fifteen (17%) patients received Insulin in the emergency ward for the management of their raised blood sugar level. Twenty three (26.1%) patients had less than 1 day of stay in the hospital, 20(22.7%) had 1to 5 days of stay in the hospital, 39(44.3%) had 6 to 10 days of hospital stay while remaining 6(6.81%) patients had hospital stay of more than 10 days.

Nine (10.2%) patients were either referred or discharged on patient's request. (DOPR) or left against medical advice (LAMA), 50(56.8%) were discharged home and 29(33%) patients expired in the hospital. The mean blood glucose in the group with admission normoglycaemia was 113.52 mg/dl while that in the group with admission hyperglycemia was 237.77 mg/dl. The mean systolic BP, diastolic BP, CK MB and CK total in group with admission normoglycaemia was 112 mmHg, 71.59 mmHg, 87.5 Units and 958.6 Units respectively while that in the

Table No. 2: Gender, insulin at ER, mortality and Days of hospital stay among STEMI pts:

		Hyperglycaemia	Normoglycaemia	P value
Total Number(N=60)		N=30	N=30	
Gender	Male(%)	21(70)	8(26.7)	
	Female(%)	9(30)	22(73.3)	0.001
Insulin at ER (%)		8(26.7)	0	0.002
Mortality (%)		14(46.7)	5(16.7)	0.01
Days of Hospital stay	Min-Max	1-15	1-13	
	Mean(SD)	4.77(3.7)	5.7(3.3)	
	Median	5.00	6.00	0.170

group with admission hyperglycaemia was 129.55mmHg, 79.45mmHg, 107.95 Units, 755.41 Units respectively.

2.2 Gender, insulin at ER, mortality and days of hospital stay among STEMI patients: Among 60 patients who presented with STEMI, 30(50%) had admission blood glucose > 140mg / d * l and remaining 30(50%)

had admission blood glucose </= 140mg / d * l . Male were more likely to present with admission blood glucose > 140mg / d * l than Females (p = 0.001) Patients presenting with admission blood glucose > 140mg / d * l were more likely to receive insulin at ER (p = 0.002) The mortality in the group with admission blood glucose > 140mg / d * l was more as compared to the group with admission blood glucose </= 140mg / d * l (p = 0.012) The minimum and maximum days of stay among group with admission blood glucose >140mg/dl was 1 and 15 respectively while that among the group with admission blood glucose </= 140mg / d * l was 1 and 13 respectively. The mean days of stay, SD and Median among the group with admission blood glucose > 140mg / d * l was 4.77, 3.7 and 5.00 while that among the group with admission blood glucose </= 140mg / d * l was 5.7, 3.3 and 6(p > 0.05).

Table No. 3: Gender, insulin at ER, mortality and Days of hospital stay among NSTEMI pts:

		Hyperglycemia	Normoglycemia	P values
Total Number(N=21)		N=10(47.6%)	N=11(52.4%)	
Gender	Male(%)	7(70)	3(27.3)	
	Female(%)	3(30)	8(72.7)	0.050
Insulin at ER(%)		5(50)	0	0.007
Mortality(%)		5(50)	5(45)	0.835
Days of Hospital stay	Min-Max	1-9	1-12	
	Mean(SD)	4.9(3.24)	4.73(3.90)	
	Median	6.5	6.0	0.716

2.3 Gender, insulin at ER, mortality and days of hospital stay among NSTEMI patients: Among 21 patients who presented with NSTEMI, 10(47.6%) had admission blood glucose >140mg/dl while 11(52.4\%) had admission blood glucose c/=140mg/dL There was no statistical difference between the two groups with regards to Gender. Patients presenting with admission blood glucose >140mg/dl were more likely to be treated with Insulin at ER but there was no comparable difference with regards to mortality in the two groups. The mean days of stay among patients presenting with admission blood glucose >140mg/dl was 4.9 with SD 3.24 and that among Patients presenting with admission blood glucose </=140mg/dl was 4.73 with SD 3.90. The minimum day of stay is 1 in both groups whereas patients presenting with admission blood glucose </=140mg/dl were more likely to be having longer hospital stay although it is not significant statistically (p>0.05). The median of hospital stay was 6.5 and 6.0 days among patients presenting with admission blood glucose >140mg/dl and </=140mg/dl respectively.

Table No. 4: Gender, insulin at ER, mortality and Days of hospital stay among UA pts:

		Hyperglycemia	Normoglycemia	P values
Total Number(N=7)		N=4(57.1%)	N=3(42.9%)	
Gender	Male(%)	3(75)	1(33.3)	
	Female(%)	1(25)	2(66.7)	0.27
Insulin at ER(%)		2(50)	0	0.147
Mortality(%)		0	0	-
Days of Hospital stay	Min-Max	5-12	3-4	
	Mean(SD)	8.50(3.10)	3.33(0.57)	
	Median	8.5	3.0	0.001

2.4 Gender, insulin at ER, mortality and days of hospital stay among UA patients: Among 7 patients having Unstable Angina, 4(57.1%) had admission blood glucose >140mg/dl while 3(42.9%) had admission blood glucose </=140mg/dl. There was no significant difference in number between the patients receiving and not receiving insulin at ER among the two groups. No mortality was noted among the UA patients. Patients of UA presenting with admission blood glucose >140mg/dl were more likely to have longer hospital stay than those presenting with admission blood glucose </=140mg/dl ($p<0.05$). The minimum and maximum days of stay among group presenting with admission blood glucose level> 140 mg/dl is 5 and 12 with a mean of 8.5 (SD=3.10) while minimum, maximum and mean days of stay in group with admission blood glucose level </=140 mg/dl is 3, 4 and 3.33 (SD=0.57). Patients with admission blood glucose level 140 mg/dl were more likely to have longer hospital stay.

Table No. 5: Gender, admission BG, insulin at ER, mortality and hospital stay among diabetics with ACS:

		Hyperglycemia	Normoglycemia	P values
Total Number(N=25)		N=22	N=3	
Gender	Male(%)	16(72.7)	1(33.3)	
	Female(%)	6(27.3)	2(66.6)	0.170
Admission BG	Min-Max	156-481	94-111	
	Mean(SD)	282.36(90.27)	105(9.53)	
	Median	255	110	0.006
Insulin at ER(%)		15(68.2)	0	0.052
Mortality(%)		9(40.9)	1(33.3)	0.654
Days of Hospital stay	Min-Max	1-12	1-9	
	Mean(SD)	4.77(3.65)	6.00(4.35)	
	Median	4.5	8.0	0.577

2.5 Gender, admission blood glucose, Insulin at ER, mortality and hospital stay among diabetics with ACS: Among 25 diabetic patients presenting with ACS, 22 (88%) had admission blood glucose >140mg/dl while 3(12%) had admission blood glucose </=140mg/dl. Male diabetics were more likely to present with admission blood glucose 140mg/dl than female diabetics (p>0.05). Among the group with admission Blood glucose 140 mg/dl, the Minimum, Maximum and Mean BG during admission was greater than that in the group with admission blood glucose <=140 mg/dl. Although more diabetic patients with admission hyperglycaemia died as compared to the diabetics with admission normoglycaemia, statistical Significance was not established (p>0.05). The minimum day of hospital stay among the two groups was 1 but the maximum length of hospital stay was more among the patients presenting with admission blood glucose >140mg/dl. The mean days of hospital stay was more in the group having admission blood glucase</=140mg/dl. The mortality between the diabetics and non diabetics (or whose diabetic status was not known) who presented with admission blood glucose level >140mg/dl was similar.

Table No. 6: Gender, Age, days of stay and mortality among ACS patients receiving and not receiving Insulin at ER:

Total Number(N=15)		Received Insulin at ER	Did not receive Insulin at ER	P values
Gender	Male(%)	N=11(73.1)	N=32(43.8)	
	Female(%)	4(26.7)	41(56.2)	0.037
Days of stay	Min-Max	1-12	1-15	
	Mean(SD)	4.73(3.93)	5.32(3.46)	
	Median	4.00	6.00	0.574
Age (yrs)	Min-Max	45-77	33-90	
	Mean(SD)	61.2(9.1)	64.3(12.88)	
	Median	61	65	0.345
Mortality(%)		7(46.7)	22(53.3)	0.215

2.6 Gender, Age, days of stay and mortality among ACS patients receiving and not receiving Insulin at ER: All total of 15 patients received insulin in the ER among which 11(73.2%) were male and 4(26.7%) were female. Male patients were more likely to receive insulin in the ER than the female patients ($p<0.05$). Although statistically insignificant, the maximum days of hospital stay was more in the group who did not receive insulin in the ER

(p>0.05). The mortality among the group receiving insulin at ER was 7(46.7%) while that among the group who did not receive insulin in the emergency ward was 22(53.3%) (p>0.05).

3. DISCUSSION

Admission hyperglycaemia is common in patients with ACS and is regarded as stress induced which leads to various catecholamine release and sympathetic activation during the episode stimulating gluconeogenesis, glycogenolysis and lipolysis.[16][17] Admission hyperglycaemia in ACS patients is regarded as a bad prognostic marker with regards to in-hospital and long term all cause mortality.[16] In some of the large studies involving randomized controlled trials, it has been demonstrated that, the initial mean 24-hour and mean hospitalization glucose levels >120-140 mg/dL is associated with increase in short-term and long term mortality risk.[45] In our study, it has been found that almost 50% of ACS patients presenting to the emergency have blood sugar level >140mg/dl which is comparable to the previous studies done by P. Deedwania et al.[18] A study done by D. Mudespacher et al has shown that 47% of ACS patients had normal admission blood sugar level.[34] Anetta U et al has also stated that almost 50% of STEMI patients have admission hyperglycaemia.[46] As far as that in male and female is concerned, in a study by D Mudespacher et al, it has been demonstrated that male patients with ACS presenting with high admission blood sugar level was 68.1% as compared to the female patients which was 31.9%.[34] In our study also, the male patients with ACS were more likely to present with admission hyperglycaemia than the female patients (70.5% Vs 29.65%) which is comparable to the previous study.

Patients with admission hyperglycaemia in our study are more likely to present with blood pressure >/=140/90 mm hg. Both the systolic and diastolic blood Pressures are high in patients presenting with admission hyperglycaemia. Same result has been demonstrated by a study done by Marfella R et al. where they have shown that ACS patients with newly diagnosed hyperglycaemia have slightly increased systolic as well as diastolic blood pressure during presentation.[47] This result is more likely be due to the fact that the release of catecholamines and activation of the sympathetic nervous system occurs during the stress situation leading to stress hyperglycaemia and increased blood pressure.[23] ACS patients presenting with admission hyperglycaemia and admission BP-140/90mmHg were more commonly past hypertensive and have significantly high in-hospital mortality (p<0.05). This may be due to the long term effect of unknown and uncontrolled hypertension leading atherosclerotic changes and various major organ dysfunctions. Moreover, hypertension itself is a risk factor for ACS which could have add-on effect on the detrimental effect caused by coronary vaso occlusion.

Comparable number of patients in the two groups, in our study, have presenting symptoms as chest pain(84%), epigastric pain, SOB and nausea/vomiting which are typical to ACS which is similar to a study done by D Mudespacher et al. who have demonstrated that atypical symptoms are present in 13-21% of patients.[34]

In our study, the number of patients presenting with admission hyperglycaemia who were current smokers is less compared to those presenting without admission hyperglycaemia who smoked currently, though the result is statistically not significant. CP Pinheiro et al. conducted a study in Brazil and have demonstrated that 9(13.6%) patients were current smokers who were hyperglycaemics and 15(17.6%) patients were current smokers but were normoglycaemics.[17] Although the ratio of smokers among the hyperglycaemics and normoglycaemics are comparable to our study, the percentage of patients who are current smokers is more than the study that is done by CP Pinheiro et al. This difference in smoking habits may be due to the fact that smoking habit is directly related to the socioeconomic and educational status of a country. Nepal has low socioeconomic status as compared to Brazil and there are higher number of less educated people here.[48] In the patients who smoked, the mean pack year in admission hyperglycaemia group is 3.95(SD 7.48) and that in normoglycaemia group is 4.66(SD8.18).

In our study, troponin I is positive in a comparable number of patients with and without admission hyperglycaenia. As compared to higher KILLIP class, patients presenting with KILLIP class I are more likely to present with admission nonoglysarmia (p=0.05). Similar study done by S. Rocha et al have demonstrated that higher the admission glucose, it was more probable that KILLIP class was more than I.[49] Higher the KILLIP class, more severe is the stress and hence the stress hyperglycaemia.[30][34] Hence, it can be the reason as to why KILLIP class I patients are likely to present with admission blood glucose level </=140 mg/dl compared to higher KILLIP class.

Patients with known history of systemic hypertension and diabetes were more likely to present with admission hyperglycaemia from our study. 72.9% known hypertensives and 88% known diabetics presented with admission hypertension (p<0.01). As a very high number of patients have undiagnosed metabolic syndrome in Nepal, it is possible that those who are diagnosed hypertension may have concomitant diabetes as well[50] which is undiagnosed.

In this study, the number of STEMI, NSTEMI and UA patients having hyperglycaemia and normoglycaemia during admission are approximately equal. In the two groups, maximum number of patients have STEMI followed by NSTEMI and finally UA in that order of presentation. It is in contrast to a Study conducted by Silvia M. et al who have shown that the number of ACS patients with admission hyperglycaemia are in the order NSTEMI>STEMI>UA.[51]

The number of patients with admission hyperglycaemia treated along with PCI and medical management are 15 (31%) and those with admission normoglycemia treated with PCI as well as medicine are 21(47.7%) in our study. Among the total mortality of 29(32.9%), 23(79.3%) patients died who did not receive PCI and were managed on medical management alone whereas only 6(20.3%) patients died who were treated with medicine as well as PCI. The overall mortality following ACS has been significantly reduced in the patients in whom medical management as well as PCI is the modality of treatment (p=0.007). This reduction after PCI can be due to the fact that PCI has been regarded superior to medical management or fibrinolysis alone because PCI offers better vessel patency and perfusion with less reinfarction, less risk of intracranial hemorrhage and improved survival regardless of lesion location or patient age.[52] Although there was less death following PCI in the group with admission hyperglycaemia, it was statistically insignificant (p>0.05).

In the group with admission hyperglycaemia, in our study, 20(45.4%) patients have been discharged home while 30(68.1%) patients are discharged in the group with admission blood glucose level </=140 mg/dl (p<0.05). Hence, significant number of patients has been discharged home who presented with admission normoglycaemia, It has already been proved by various studies that admission hyperglycaemia is a risk factor for adverse outcome in ACS patients. P Panduranga et al., after multivariate adjustment, showed that severe hyperglycemia was associated with higher in-hospital mortality when compared with both euglycaemia and mild hyperglycaemia.[53] D Mudespacher et al have shown that in-hospital mortality increased from 3% in normoglycaemia group to 15% in hyperglycemia group.[34] P Deedwania et al. have also demonstrated that admission hyperglycemia patients have increased in-hospital mortality and major adverse cardiac events.[18]

The Mean age of presentation in group with admission hyperglycaemia is 62.84 years with SD 11.41 whereas that with admission normoglycaemia group is 64.98 years with SD 13.23. The minimum and maximum age of presentation in group with admission hyperglycaemia was 33 and 82 years respectively. The age of the patients in admission normoglycaemia group ranged from 40 years to 90 years. A study done by M Koshiborod et al. has shown the mean age of presentation with normoglycaemia to be 76.5 years with a SD of 7.5 while that with hyperglycaemia (>140mg/dl) to be 76.9 years with SD of 7.5.[38] Another study done by JR Timmer et al. have shown the mean age of presentation in hyperglycemic group to be 68.0 (SD 11.2) and that in normoglycaemia group to be 62.8 (SD 13.2).[32]

In our study, the mean blood glucose level in admission hyperglycaemia group is 237.77 mg/dl (SD83.68) while that in admission normoglycaemia group is 64.98 mg/dl (SD 19.99). The minimum blood sugar level in admission hyperglycaemia group is 143mg/dl while that in admission normoglycaemia group is 56 mg/dl. The maximum blood sugar level in admission hyperglycaemia group is 481mg/dl whereas in admission Normoglycaemia group is 140mg/dl. A study done by Mansaur AA et al has shown that the mean blood glucose level in hyperglycaemia group was 191.3 (SD 66.7) whereas in normoglycaemia group was 111.6 (SD 16.1).[54] which is far in contrast to our study. High blood sugar in Nepalese during presentation may be due to the fact that Nepalese have a high prevalence of diabetes and hyperglycaemia which is still under diagnosed and even if diagnosed, it is not well managed due to lack of education and exercise and hence present with very high levels.[50] The mean CK MB and CK Total were comparable in the two groups with a high degree of deviation from the mean.

From our study, the mean days of stay in the group with admission hyperglycaemia has been found to be 5.14 days (SD 3.68) and that in the group with admission normoglycaemia is found to be 5.30 days (SD 3.40), The mean hospital stay is slightly less in this study as compared to the study done by CP Pinheiro et al where the mean hospital stay has been shown to be 8.3 ± 10.2 days in hyperglycemic group and 7.2 ± 5.7 in normoglycaemia group.[17] Cause of less days of hospital stay in our study can be ascribed to the fact that the socio- economic status is low in Nepal where longer hospital stay including ICU/CCU can be a economic burden to the patients and hence were discharged home early mostly on the patient's request. In both the groups, the maximum and minimum days of in hospital stay was comparable.

Among 20 patients presented with KILLIP III/IV, 11 (55%) patients died ($p<0.05$). Hence it was likely that overall mortality be high with KILLIP class III or more. It has already been well established that higher the KILLIP class, higher is the mortality in ACS.[55]

3.1 Comparison among STEMI/NSTEMI/UA patients:

Among the 60 STEMI patients in our study, 30 patients presented with admission hyperglycaemia and 30 presented with normoglycaemia. Male patients with STEMI were more likely to present with admission hyperglycaemia (70% male Vs 30% female) and female patients were more likely to present with normoglycaemia during admission (73.3% female vs 26.7% male). This result is in contrast to a study conducted by JR Timmer et al. where they have shown that hyperglycaemia groups were more often women,[57] CP Pinheiro et al have also shown that female patients with STEMI were more likely to have hyperglycaemia during admission than the male patients.[17] Male patients were more likely to present with admission hyperglycaemia as compared to female which has been explained by a study done by P Karki et al. in the eastern part of Nepal which has shown that the prevalence of NIDDM in females was relatively lower than in males.[57] Our study shows that none of the patient presenting with admission normoglycaemia has received insulin in the ER. 26.7% of STEMI patients presenting to the ER with hyperglycaemia have received insulin.

All total of NSTEMI patients are 21 among which 10(47.6%) were hyperglycaemics whereas 11(52.4%) are normoglycaemics during admission. Although statistically insignificant, male patients were more likely to present with hyperglycaemia than the female patients. This result is in contrary to the findings that has been shown by JY Takada et al where they have shown that male patients were more likely to present with normoglycaemia than the female patients.[31] As larger number of diabetic patients were male (17 Vs 8; Male Vs Female), it was likely that more male patients would present with hyperglycaemia as evident from our study. 5 of 10 NSTEMI with hyperglycaemia received insulin in the ER. In hypoglycaemic and normoglycaemic groups the mean days of stay was 4.9(SD 3.24) and 4.73(SD 3.90), maximum days of hospital stay was 9 days and 12 days respectively with the minimum hospital stay of 1 day in both the groups respectively. A study done by et al have shown that the mean

hospital stay of 9 ± 0.7 days in newly diagnosed hyperglycanmuia and 4.5 ± 0.1 days in normoglycaemia,[58] There is lesser mean hospital stay in the hyperglycaemia group from our study.

UA patients were 7 in number where 4 (57.1%) presented with hyperglycaemia among which 3 (75%) were male whereas, 3(42.9%) presented with narmoglycaemia and 2(66.7%) were female. Study done by Taysir S. Garadah et al has shown that 63% of male were in normoglycaemia group while 62.5% were in hyperglycaemia group which is more or less stmilar to our study[59], among the hyperglycaemia, 2(50%) received insulin and no mortality was observed in any group of patients. The mean hospital stay was less in normaglycaemia group as compared to hyperglycaemia group which was comparable with a study done by JY Takada et al.[31]

3.2 Mortality comparison among STEMI/NSTEMI/UA patients:

As far as mortality is concerned, overall mortality is 19 among 60 patients (i.e. 31.6%) in STEMI while that in NSTEMI is 10 among 21 patients (i.e. 47.6%) in our study. Hence, mortality rate among NSTEMI is high as compared to STEMI although it is statistically not significant. The overall mortality in our study is in contrast to a study done by JY Takada et al. who have demonstrated less overall mortality among the two groups (3.8% Vs. 5% among STEMI Vs. NSTEMI) although the ratio of mortality between the two groups was comparable.[31] In addition to the illiteracy, markedly delayed presentation of ACS to the ER, lack of adequate resources and logistic difficulties for a timely PCI could explain high overall mortality[57], Low education status has been recognized as a very consistent factor for the increased mortality in ACS[60]. Differing to our finding, D Mudespacher et al have demonstrated higher mortality rate in STEMI than in NSTEMI.[34]

Mortality in NSTEMI is 5 (50%) in hyperglycaemia group and 5(45%) in normoglycaemia group ($p>0.05$) while that in STEMI is 46.7% in hyperglycaemia group and 16.7% in normoglycaemia group in our study. Hence, there is no significant difference in mortality among hyperglycaemia and Normoglycaemia in NSTEMI whereas significantly high mortality is noted among STEMI with hyperglycemia than STEMI with normoglycaemia ($p=0.01$). STEMI patients with admission hyperglycaemia are more likely to have more in-hospital death than those with normoglycaemia (46.7% vs 16.7% at $p=0.01$) which may be due to the fact that hyperglycaemia on admission was associated with large area at risk and large infarct size in the myocardium leading to increased mortality[30], Although STEMI with hyperglycaemia had higher mortality rate in our study, JY Takada et al have stated that admission blood glucose was not an independent factor in determining the in-hospital mortality among STEMI.[31] This finding was different from other studies done by Straumann Eet al[61] and Hoebers LP et al.[62]

3.3 Mortality among diabetics and non-diabetics:

Overall mortality among the diabetics is 40.9%, that in non diabetics was 30.15% in our study. The overall in-hospital mortality rate is different to a study done by D Mudespacher et al. who found out 10% overall in-hospital mortality in diabetics.[34] Higher overall mortality in our study may again be due to the fact that Nepalese have low socioeconomic status and illiteracy which may be the cause for delayed presentation leading to various life threatening complications.[63] In our study, total diabetics are 25 among which 22 (88%) presented with hyperglycemia and 3 (12%) presented with normoglycaemia. Mean, minimum and maximum admission glucose is 282.36 (SD 90.27), 156 and 481mg/dl among admission hyperglycaemia group while it was 105 (SD 90.27), 94 and 111mg/dl among normoglycaemia group respectively. The mortality among the diabetics with admission hyperglycaemia is 9(40.9%) while the mortality among admission normoglycaemia group is 1(33.3%) in our study. The mortality among non diabetics with hyperglycaemia is 10(52.6%) and that with normoglycaemia was 9(47,4%). Although statistically non significant, the mortality is higher in hyperglycaemia with non diabetes than that with diabetes. Wahab et al, have stated that the non diabetics with hyperglycaemia have a concealed, prolonged and untreated diabetes which may be later diagnosed on serial follow ups.[64] The finding were in accordance with a study done by D Madespacher et al who have demonstrated that non-diabetics with admission hyperglycaemia had a non significantly higher major adverse cardiac event rate and in-hospital mortality compared to diabetic patients.[34]

Although it has also been stated in various studies that admission hyperglycaemia is associated with increased mortality in diabetics[35][43][44][61][64][65]and non diabetics as well.[35][43][44][61][64][65]

3.4 Mortality among patients receiving and not receiving insulin at ER:

All total of 15 patients received insulin in the ER and all of these patients have hyperglycaemia during presentation in our study. More the hyperglycaemia, more was the chances of receiving insulin in the ER ($p<0.01$) which is similar to a study done by Mudespacher D.[34] There is no significant difference between the mean hospital stay and mean age (in years) among who received insulin and who didn't. The mortality is insignificantly higher in those who did not receive insulin than those who received. Similar to our finding, C Weston et al have demonstrated in a study of non-diabetic patients having ACS and hyperglycaemia that, the treatment with insulin was associated with a reduction in the relative risk of death, evident within 7 days of admission, which persists at 30 days 20 Hence, treatment of stress hyperglycaemia in the emergency could be beneficial at least to reduce in-hospital mortality. Bringing back the stress hyperglycaemia to normal levels may help reduce the oxidative stress and decrease the production of free radicals and hence the mortality.[30]

CONCLUSIONS

The data from this study have shown that hyperglycaemia at admission is very common in acute coronary syndrome patients. Admission hyperglycaemia is a significant predictor of in-hospital mortality. Male patients were more likely to present with admission hyperglycaemia and hence could be at higher risk of in- hospital mortality. Diabetics and hypertensives with ACS had more chances to present with admission hyperglycaemia and thus could be at special risk. These patients may benefit from an appropriate treatment strategy, including strict glycaemic control on presentation to the Emergency ward. Further studies to evaluate the effect of acute and intensive glycaemic control on reducing in- hospital mortality in patients admitted with ACS are needed.

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