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ELEVATED GLYCOSYLATED HEMOGLOBIN IS HARBINGER OF ADVERSE SHORT-TERM OUTCOMES FOLLOWING CORONARY ARTERY BYPASS GRAFTING

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Contribution
KT conceived the idea and designed the study. Data collection and manuscript writing was done by KT, SAK, IT, AA, HB, VU, KZ, ARM, and PAC. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To determine the association of elevated HbA1c levels with length of ICU stay, prolonged mechanical ventilator and ionotropic support, and infections in diabetic patients undergoing CABG.

Methodology: This Prospective cohort study was conducted at National Institute of Cardiovascular Diseases, Karachi. One hundred fifty eight (158) diabetic patients were enrolled fulfilling inclusion criteria. Data was classified into two groups, Exposed group: elevated HbA1c (≥7%) and Un-exposed group: HbA1c (<7%) and study outcomes in both groups were compared for any statistically significant difference.

Results: Total 86.1% patients had prolonged ICU duration, 79.7% ($p<0.001$) had prolonged mechanical ventilator and 87.3% ($p<0.001$) patients with prolonged ionotropic support in Exposed group (elevated HbA1c). In Un-exposed group (controlled HbA1c), 44.3% patients had prolonged ICU duration, 12.7% patients had prolonged mechanical ventilator and 64.6% had prolonged ionotropic support. In group-A, 35.4% were observed with sepsis, 16.5% with pneumonia and 31.6% ($p=0.026$) were with urinary tract infection while in group-B, 49.4% were with sepsis, 16.5% pneumonia and 16.5% urinary tract infection.

Conclusion: Elevated HbA1c level is risk marker for higher rate of infections and hospital length of stay after CABG. An HbA1c of 7% or greater was found to be a strong predictor of a length of ICU stay, ventilator support and adverse short-term outcomes including urinary tract infections.

Keywords: elevated pre-operative glycosylated hemoglobin, adverse short-term outcomes, coronary artery bypass graft

INTRODUCTION

In a world of finite health care resources with ever increasing demand for medical services, clinicians usually need to identify patients at risk of requiring a long period of high dependency care after cardiac surgery.[1] with factors which could anticipate adverse outcomes so that a better management strategy can be planned out. CABG being most commonly performed is considered the bread and butter of cardiac surgery.[2,3] Several factors have been marked which can predict the adverse outcome following CABG, infact early detection of patients who are likely to end up for an increased postoperative length of stay (LOS) following CABG would allow operations to be planned strategically, maximizing the chance of the availability of the ICU beds for other critical patients, not only that it can help prevent the cancellations of operations. In addition, prolonged hospital stay in patients undergoing CABG increases overall hospital costs.[4] Glycosylated hemoglobin levels indicate average blood glucose levels over the past three months, elevated level is a marker for worse prognosis, whether or not there is diagnosis of diabetes.[5-8] Glycosylation process of red blood cells is regulated by level of glucose in blood. During the lifespan of red blood cells, (90 to 120 days), constant cellular turnover and fluctuating blood glucose levels set about a proportion of HbA1c (normal range 4.0-5.9%) within the blood being glycosylated. Hence an estimation of the percentage of glycosylated hemoglobin is suggestive of the patient's blood glucose levels over three to four months which is distinctively more informative and reliable than snapshot of blood glucose reading which is liable to change and may vary depending on alteration in diet and metabolism.[5]

Pooled data has emphasized that raised HbA1c level is linked with worse postoperative outcomes including increased mortality and morbidity both long term and short term,[7,9] acute renal injury, sternal wound infection, cerebrovascular events, new onset atrial fibrillation, myocardial infarction,[5] and readmission rates.[8] In spite of already documented risk, no cardiac surgical risk scoring system, including The Society of Thoracic Surgery score, incorporates HbA1c as a risk predictor for surgical morbidity and mortality. In a prospective study done by Halkos and colleagues[5] in 3555 patients, it was reported that HbA1c more than 8.6% is linked with four times increase in hospital mortality rates. It is worth optimizing HbA1c levels particularly in elective cases. Researchers have depicted that reduction in HbA1c, by as little as 1%, results in reduced microvascular complications and lesser cardiovascular events.[9-11] The objective of this study is to determine the association of elevated pre-operative glycosylated hemoglobin with adverse short term outcomes in diabetic patients undergoing CABG operation at a tertiary care hospital in a developing country with handful resources.

METHODOLOGY

This Prospective Cohort study was conducted in Cardiac Surgery Department of National Institute of Cardiovascular Diseases (NICVD) Karachi after acquiring approval from ethical review board. Consecutive diabetic patients, of either gender, aged between 30 to 80 years undergoing CABG were enrolled. However, patients with history of previous CABG, open heart surgery, patients undergoing CABG on beating heart, concomitant CABG and valvular surgery were excluded from the study.

Prior to inclusion the purpose of the study was explained to all the patients. Informed consent was acquired by the principal investigator from all patients. Patients with HbA1c level ≥7 were allocated to exposed group and those with HbA1c level <7 were allocated to un-exposed group. Preoperative laboratory assessment, echocardiographic assessment and angiography were performed by experienced cardiologist for all patients scheduled for CABG. Modified Yale insulin infusion protocol was used for all patients to maintain a target glucose goal of 150 to 179 mg/dL in the ICU with hourly glucose monitoring and insulin titration. CABG was performed by experienced cardiac surgeons with working experience of more than five years. The general anesthesia, surgical procedure and cardiopulmonary bypass perfusion (CPB) methods were similar for all of the patients. Baseline characteristics of the patients were already recorded like gender, age, weight (kg), height (cm), and NYHA class. BMI calculated for all patients using the formula BMI = (weight kg)/(height m)2. Pre-operative HbA1c levels (%) was recorded based

on laboratory assessment. History of the patients were taken regarding DM, hypertension, and smoking status. Left ventricular ejection fraction (LVEF %) was recorded after assessing on echocardiography for all patients. Duration of CPB and aortic cross-clamping (XCT) was recorded in minutes for all patients.

Elevated pre-operative HbA1c level, Intensive Care Unit (ICU) length of stay in days (LOS), mechanical ventilator and ionotropic support in hours, and post-operative sepsis (including line infections, surgical site infections) along with pneumonia and urinary tract infection (UTI) were recorded by principal investigator. Confounding variables and biasness were well controlled by strictly following inclusion and exclusion criteria and stratification. Data was collected on pre-designed structured proforma. Patient information was kept secured and available to authorized person only throughout the study.

Data was entered and analyzed using SPSS version-21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Data were classified into two groups, exposed group: (HbA1c ≥7%) and un-exposed group: (HbA1c <7%) and study outcome in both groups was compared for any statistically significant differences and relative risk (RR) was also calculated. Descriptive statistics such as mean ± standard deviation (SD) were calculated for quantitative (continuous) variables and appropriate independent sample t-test or Mann–Whitney U test was applied to check the significant difference. Frequency and percentages were calculated for categorical variables such as age groups, gender, BMI categories, NYHA class, co-morbid conditions i.e. hypertension, and smoking and prolonged ICU length of stay (LOS), mechanical ventilator support, and ionotropic support. Effect modifier like gender, age, smoking, NYHA class, BMI categories, LVEF (%), CPB Time, aortic clamp time and comorbid conditions i.e., hypertension, and smoking were controlled through stratification. Post stratification appropriate Chi-square test or Fisher exact test was applied and relative risk (RR) was calculated. Two-sided p-value of ≤0.05 was taken as criteria of statistical significance.

RESULTS

A total of 158 diabetic patients of either gender were enrolled for this study in 1:1 ratio of patients in Exposed group (elevated HbA1c) and Un-exposed group (HbA1c) with 79 patients in each group. There were 68.4% male and 31.6% female patient in group A while in group B, there were 70.9% male and 29.1% females. The overall mean age of patients in exposed group and un-exposed group was 62.87±7.24 years and 62.53±6.86 years respectively. It was observed that, all the patients in exposed group had uncontrolled diabetes mellitus, 44.3% were hypertensive and 20.3% were smokers, while in un-exposed group, 53.2% of the patients had HbA1c levels >6.5% but less than 7%, 54.4% were hypertensive and 17.7% were smokers. Frequency distributions and detailed descriptive statistics of general characteristics including overall preoperative hbA1c, mean LVEF, CPB time and aortic clamp time of patients are presented in Table-1.

Table 1: Demographic and clinical characteristics

	Exposed group	Un-exposed group	P-value
Total (N)	**n=79**	**n=79**	
Gender			
Male	68.4% (54)	70.9% (56)	0.729
Female	31.6% (25)	29.1% (23)	
Age (years)	62.9 ± 7.2	62.5 ± 6.9	
≤ 65 years	60.8% (48)	62% (49)	0.870
>65 years	39.2% (31)	38% (30)	
Weight (kg)	86.9 ± 11	80.5 ± 10.4	<0.001
Height (cm)	165.1 ± 9.4	171.1 ± 7.5	<0.001
BMI (kg/m^2)	26.4 ± 3.4	23.6 ± 3.2	<0.001
Normal	31.6% (25)	62% (49)	0.001
Overweight	53.2% (42)	31.6% (25)	
Obese	15.2% (12)	6.3% (5)	
NHYA class			
Class I	17.7% (14)	25.3% (20)	<0.001
Class II	82.3% (65)	50.6% (40)	
Class III	0% (0)	24.1% (19)	
Co-morbid			
Hypertension	44.3% (35)	54.4% (43)	0.203
Smoking	20.3% (16)	17.7% (14)	0.685
HbA1c(%)	9.7 ± 1.5	6.1 ± 0.6	<0.001
LVEF (%)	49.2 ± 10.9	49.4 ± 13.2	0.942
Use of internal	91.1% (72)	92.4% (73)	0.772

mammary artery			
CPB Time (minutes)	119.6 ± 15.2	109.8 ± 13.9	<0.001
Aortic Clamp Time (minutes)	94.4 ± 14	83.6 ± 18.4	<0.001

The overall mean ICU stay, mechanical ventilator duration and ionotropic support in exposed group was 3.70±1.11 days, 28.05±8.29 hours and 32.71±6.57 hours respectively while in un-exposed group, mean ICU stay, mechanical ventilator duration and inotropic support was 2.58±0.76 days, 17.76±6.68 hours and 26.95±11.90 hours respectively. The detailed descriptive statistics of CU stay, mechanical ventilator duration and inotropic support are presented in Table-2.

In our study, 86.1% patients were found with prolonged ICU duration, 79.7% patients with prolonged mechanical ventilator and 87.3% patients with prolonged ionotropic support in exposed group. While in un-exposed group B, 44.3% patients were found with prolonged ICU duration, 12.7% patients with prolonged mechanical ventilator and 64.6% patients with prolonged ionotropic support. In group A, 35.4% were found with sepsis, 16.5% with pneumonia and 31.6% with urinary tract infection while in group B, 49.4% were found with sepsis, 16.5% with pneumonia and 16.5%with urinary tract infection as presented in Table-2.

The results showed that there was significant association of elevated HbA1c with prolonged ICU stay (p=0.000), mechanical ventilator (p=0.000), prolonged ionotropic support duration (p=0.001) and Pneumonia (p=0.026).

Table 2: Post-surgical in-hospital outcomes

	Exposed group	Un-exposed group	Relative Risk (95% CI)	P-value
Total (N)	**n=79**	**n=79**	**-**	**-**
ICU stay (days)	3.7 ± 1.1	2.6 ± 0.8	7.8 (3.6-17.0)	<0.001*
Prolonged stay (>2 days)	86.1% (68)	44.3% (35)		<0.001*
Mechanical ventilator duration (hours)	28.1 ± 8.3	17.8 ± 6.7	27.2 (11.5-64.3)	<0.001*
Prolonged duration (>24 hours)	79.7% (63)	12.7% (10)		<0.001*
Ionotropic support (hours)	32.7 ± 6.6	27 ± 11.9	3.8 (1.7-8.5)	<0.001*
Prolonged support (>24 hours)	87.3% (69)	64.6% (51)		<0.001*
Sepsis	35.4% (28)	49.4% (39)	0.6 (0.3-1.1)	0.077
Pneumonia	16.5% (13)	16.5% (13)	1.0 (0.4-2.3)	>0.99
Urinary Tract Infection	31.6% (25)	16.5% (13)	2.4 (1.1-5.0)	0.026*
In-hospital mortality	3.8% (3)	2.5% (2)	2.5 (0.2-9.3)	0.649

DISCUSSION

Various studies have indicated that patients with DM tend to have worse clinical consequences[12,13] with a marked increase in untoward consequences in patients post CABG. The most extensive study to date by Carson and colleagues sorted out outcomes in 41,663 patients with DM compared with those in 105,123 non-diabetic patients undergoing CABG in 434 hospitals from North America. They showed a 23% to 37% increment in 30-day and in-hospital morbidity in diabetic patients who underwent CABG.[14] It is mention worthy that Patients with DM are prone to develop postoperative infection, new-onset atrial fibrillation, renal failure than non DM patients.[15] 2011 ACCF/AHA Guideline for CABG Surgery recommends use of continuous intravenous insulin infusion to achieve and maintain an early postoperative blood glucose concentration ≤ 180 mg/dL to reduce perioperative adverse events.[16] DM is directly related with a two to fourfold higher risk of cardiovascular diseases development, moreover a three times increased risk of mortality.[17] Presently, 25% of patients undergoing coronary revascularization are diabetic.[18] Recently, the

American Diabetes Association(ADA) has included HbA1c in diagnostic criteria for diabetes mellitus.[19]

Glycosylated hemoglobin hbA1c reflects a patient's existing blood glucose levels over the period of three months. It may show lower than actual value because of hemolytic anemia, blood loss, renal issues, and drugs (e.g. erythropoietin, iron formulations). It may manifest higher levels secondary to hypertriglyceridemia, hyperbilirubinemia, alcoholism, pregnancy, and medications (e.g. salicylates etc.).[20] Certified methods for analysis recommended by the National Glycohemoglobin Standardization Program (http://www.ngsp.org) and ADA are utilized to measure HbA1c levels. It is recommended that for disease prevention the target HbA1c should fall below 7% which manifests an estimated average glucose level of 154 mg/dl (8.6 mmol/l). It is probably a better prognostic forecaster than other glucose metabolic parameters, which only show a point in time level of blood glucose in diabetic patients. Selvin and colleagues[10] demonstrated that the relative risk of cardiovascular disease increase by 18% for type 2 diabetes and by 15% for type 1 diabetes for each percent increase in HbA1c.

Improved results in diabetic patients following CABG can be accredited to adoption of secondary prevention protocol specially, use of the left internal thoracic artery (ITA), avoidance of bilateral ITAs use in diabetics, advancement in anesthesia and critical care management, encouragement of off-pump CABG techniques, perioperative insulin infusions, and postoperative antiplatelet drugs and lipid-lowering agents.

In this study, we evaluated pateints for association of elevated HbA1c levels with adverse outcomes post-CABG and we found an increase in ICU LOS, duration of mechanical ventilation, superficial wound infections and UTIs, these findings are consistent with studies presented by Halkos et al.[5], Sato et al [21], Alserius et al.[22] and Hudson et al.[23] The results of our study suggest that uncontrolled hyperglycemia (HbA1C ≥7%) is a marker of worst consequences after CABG in terms of infections, prolonged mechanical ventilation, hospital stay, acute kidney injuries and new-onset AF following surgery. A Study conducted by Finger B et al. reported infection rate of 31.58%, blood product or blood factor administration in 37.43%, cardiac arrest in 1.9%, reoperation in 10.13% of the patients, short term mortality rate of 3.51%, and ICU LOS of 76.26 ± 71.17 hours in patients with HbA1c ≥ 7%. In patients with HbA1c less than 7%, infection rate was 10.76 %, length of ICU stay was 81.85%.[24] Almogati and collegues have also demonstrated a relationship between raised HbA1c and longer hospital stay.[25]

CONCLUSION

Patients with elevated HbA1c levels are at higher risk for adverse events after CABG. An HbA1c of 7% or greater was found to be a strong forecaster of longer ICU stay and rate of infections, markedly increasing the cost burden to hospital. It is proposed that HbA1c levels can be utilized as a surrogate marker and screening tool for cardiac and non-cardiac morbidity that could possibly prolongs hospitalization after coronary artery bypass surgery. It's worth devoting time and effort to optimize HbA1c <7% to avoid unfavorable detrimental, consequences of CABG.

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