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Original Article

Hyperglycemia or High Hemoglobin A1C: Which One is More Associated with Morbidity and Mortality after Coronary Artery Bypass Graft Surgery?

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Propose: Our aim was to determine which criterion- hyperglycemia or high levels of glycosylated hemoglobin (HbA1C) is more associated with increased mortality and morbidity after coronary artery bypass graft (CABG).
Methods: Two hundred and sixteen patients who underwent elective CABG were enrolled in this prospective study. In order to compare postoperative outcomes regarding HbA1c and fasting blood sugar (FBS) levels, the patients were divided into two groups based on plasma HbA1c levels >7% or ≤7% and FBS >126 mg/dl or ≤126 mg/dl.
Results: Of 216 studied patients, 165 and 51 cases had levels of HbA1C ≤7% and HbA1c >7% respectively. Furthermore, 129 and 87 patients had levels of FBS of ≤126 mg/dl and FBS of >126 mg/dl respectively. Multivariate analyses revealed that patients with high HbA1C levels experienced significantly higher rates of postoperative re-intubation [P = 0.001, OR (95% CI) = 8.15 (2.88–23.09)], wound infection [P = 0.001, OR (95% CI) = 8.15 (2.88–23.09)] and bleeding [P = 0.027, OR (95% CI) = 2.18 (1.10–4.35)]. In addition, hyperglycemic patients had a higher frequency of arrhythmias [P = 0.001, OR (95% CI) = 3.07 (1.69–5.59)], atelectasis [P = 0.029, OR (95% CI) = 1.88 (1.07–3.30)] and wound infection [P = 0.001, OR (95% CI) = 8.75 (2.45–31.25)].
Conclusion: Higher levels of both HbA1C and FBS contribute to the increased risk of morbidity but not mortality rates in post-CABG surgery patients; yet further studies are required to distinguish "a better predictor" of postoperative adverse events.

Keywords: hyperglycemia, glycosylated hemoglobin, mortality, morbidity, coronary artery bypass graft surgery

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Introduction

Hyperglycemia is a common finding during and after coronary artery bypass graft (CABG) surgery in both diabetic and non-diabetic patients.[1,2] Previous studies have shown that clinical complications after CABG in diabetic patients are significantly worse than non-diabetic patients.[3] Preoperative high blood glucose is considered an independent risk factor for increased morbidity and mortality after surgery.[4] Being a useful indicator for glycemic abnormality so easier than the oral glucose tolerance test to be performed, glycosylated hemoglobin (HbA1c) is a sensitive and reliable biomarker in clinical practice that assesses glucose control within the previous 2–3 month period.[5] HbA1c does not show short-term glycemic changes due to the 90 to 120 day lifespan of red blood cells as HbA1c will only be eliminated when red cells are replaced.[6]

Some evidence indicates that high HbA1c levels prior to surgery are strongly associated with the severity of adverse events after CABG.[6] Preoperative HbA1c and fasting blood sugar (FBS) testing may allow for accurate risk estimation in patients undergoing CABG surgery.[7] It is not well-known whether chronic glucose homeostasis disturbance reflected by HbA1C levels or acute glycemic abnormalities revealed by FBS measurements on the day of surgery are accurately associated with adverse outcomes after CABG surgery. The purpose of this study was to determine whether HbA1C or FBS on the morning of surgery could predict probable adverse events after CABG surgery more properly. The main measured endpoints in this study were early postoperative complications in the surgical intensive care unit (ICU) and in-hospital mortality rate.

Methods

In a prospective observational research, 216 adult (≥18 years old) patients of American Society of Anesthesiologists status Class II or III who underwent cardiac surgical procedures using cardiopulmonary bypass (CPB) in a referral university hospital were studied. Required approval of the institutional ethical committee and informed written consents from all patients were obtained. Inclusion criteria consisted of all adult patients who underwent elective CABG. Patients with hepatic failure or those necessitating emergency surgery were excluded from the study. Later, the patients were divided into two groups based on their FBS levels being "higher" or "lower or equal to" 126 mg/dl; patient were also divided into two groups based on their plasma HbA1c levels "higher" or "lower or equal to".[7] Plasma HbA1c levels were measured on the average 2 days before surgery while FBS levels were assessed in the morning of surgery (fasting glucose: fasting >8 hours). A high HbA1c is an indicator of long-term glycemic control and risk of diabetes mellitus (DM) complications. However in the peri-operative period, treating patients with high HbA1C aims to keep their blood glucose levels as normal as possible and management of the related complications.

In the preoperative period, clinical history was taken, and physical examination was performed by the anesthesia service. Information collected for each patient included age, sex, New York Heart Association (NYHA) status, ejection fraction (EF), tobacco use, inotropic therapy, presence of an intra-aortic balloon pump (IABP), and co-morbidity factors [diabetes mellitus, chronic obstructive pulmonary disease (COPD), and renal insufficiency]. Elective placement of IABP was considered in high-risk patients such as those with significant left main stem disease, severe LV dysfunction (EF <30%) or dilated cardiomyopathy. Also, we used IABP in patients who failure to wean from CPB or experienced acute pulmonary edema after separation from CPB or post-operative period" refractory to medical treatment. There was no complication in our patients that treated by IABP. We weaned patients from IABP when their achieved hemodynamic stability such as a heart rate of <120 beat/min and systolic blood pressure of ≥90 mmHg without their needing inotropic agents. Throughout this study, tobacco use was defined as more than 10 cigarettes per day. The presence of COPD was defined based on the clinical history as noted in the preoperative medical records. Preoperative renal insufficiency was defined as a serum creatinine concentration greater than 2 mg/dL.

The anesthesia induction for all patients was employed using midazolam 0.05–0.1 mg/Kg, fentanyl 4–8 µg/Kg or sufentanil 0.6–0.8 µg/Kg, atracurium 0.5 mg/Kg or pancuronium 0.1 mg/Kg and thiopental sodium 1–2 mg/Kg before tracheal intubation. Later, anesthesia was maintained with infusion of midazolam, fentanyl or sufentanil, atracurium or pancuronium and isoflurane.

During the anesthesia and operation, routine monitoring included pulse oxymetry, electrocardiography, indwelling arterial catheter, central venous catheter, arterial blood gases (ABGs) analysis , hemoglobin, hematocrit, glucose, sodium and potassium levels, nasopharyngeal and rectal thermal probes and urinary catheter. All operations were performed by using CPB at mild to moderate core hypothermia (28–32°C). Myocardial protection was accomplished with intermittent antegrade or combined antegrade and retrograde saline or blood cardioplegia. Operative outcomes consisted of CPB and aortic cross clamp times.

During ICU stay, all patients were visited daily by cardiac anesthesiologists who collected the outcome data including postoperative cardiac, respiratory, renal and neurological complications. Duration of mechanical ventilation was defined as the hours with mechanical ventilation during ICU stay. The postoperative chest radiographies were studied daily for evidence of pulmonary complications such as pleural effusion, atelectasis, or pneumothorax. Evaluation of the cardiovascular status included cardiac rhythm and need to inotropic drugs or IABP to maintain hemodynamic stability. Significant arrhythmias were described as those causing hemodynamic instability and requiring treatment. The necessity of inotropic drug administration was defined as a moderate to high doses of an inotropic drug required to maintain hemodynamic stability for more than one hour. Postoperative EF was evaluated by transthoracic echocardiography (TTE) and compared with preoperative values. Bleeding was defined as blood loss ≥200 mL/h or more than 1000 mL in 24 hours. Cardiac tamponade was diagnosed by clinical examination and TTE and confirmed after re-exploration. Postoperative renal insufficiency was considered as the creatinine concentration of more than 2 mg/dL or increase in preoperative value of more than 1 mg/dL. Stroke was described as a neurological abnormality confirmed by a consultant neurologist. Infection was confirmed by positive cultures of blood, sputum, urine, plural or mediastinal fluid, and incisional discharge samples. Treatment of sepsis varied for each patient depending on the clinical course, the organs affected, and the extent of damage, however, the ICU and consultant specialists used antibiotics, treating the source of infection, such as an abscess or infected wound, vasopressors to treat low blood pressure and other modalities such as steroids or insulin, blood transfusion, mechanical ventilation and dialysis. Additional collected data included the length of ICU stay, and in-hospital mortality rate.

Statistical analysis

All study data were analyzed using the SPSS version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The study groups were evaluated to compare perioperative outcomes between elevated HbA1C (>7%) and normal HbA1C (≤7%) groups and also between elevated FBS (>126 mg/dL) and normal FBS (≤126 mg/dL) groups. To compare continuous variables between the two studied groups independent samples *t*-test and to compare categorical variables Chi-square test or Fisher's exact test were used. Binary logistic regression test was used for multivariate analysis to identify independent predictors for postoperative complications. In this study, statistically significance level was considered as $P \leq 0.05$.

Results

From January 2012 to September 2012, 216 patients (138 males and 78 females with the mean age of 64 ± 10.2 years and the range between 39–85 years) undergoing elective CABG procedure in our institute were included. Of the 216 patients, 141(63.3%) were non-diabetic, and 75(37.7%) were diabetic. Also, 165(76.4%) patients had normal HbA1C (≤7%) and 51(23.4%) had high HbA1c (>7%) levels. Of 51 patients with high HbA1c levels, 12 patients were non-diabetic, and 39 patients had diabetes mellitus. **Table 1** shows baseline characteristics and preoperative factors according to HbA1c and FBS levels subgroups. Group with elevated HbA1c level had a higher percentage of female patients, higher body mass index ($P = 0.005$) and a higher percentage of left main (LM) coronary artery stenosis ($P = 0.001$).

In-hospital outcomes are summarized by HbA1c and FBS levels subgroups in **Table 2**. Some of the complications like congestive heart failure (CHF), need to IABP, re-intubation, sepsis, wound infection, massive bleeding (>1000 mL/24h) and multi-organ failure had a significant association with elevated HbA1c levels. There were not statistically significant association between high levels of HbA1C or FBS and in-hospital mortality rate in our studied patients (**Table 2**).

Binary logistic regression models were used to show the association between HbA1c >7% and some of the postoperative complications (**Table 3**). Furthermore, multivariate analysis showed that FBS >126 mg/dL had statistically significant association with some of the postoperative complications such as arrhythmia, atelectasis and wound infection (**Table 4**).

Discussion

The aim of this study was to determine if either higher HbA1c or FBS levels are of better association with

Table 1 Demographic and clinical characteristics according to HbA1C and FBS levels

	A1cHb ≤7 (n = 165)	A1cHb >7 (n = 51)	p	FBS ≤126 mg/dl (n = 129)	FBS >126 mg/dl (n = 87)	p
Age (year)	64.3 ± 10.9	63.8 ± 8.2	0.291	65.35 ± 10.18	62.45 ± 10.23	0.042
Sex (M/F)	117/48	21/30	0.001	90/39	48/39	0.021
Weight (kg)	72.4 ± 11.1	75.4 ± 9.7	0.077	72.65 ± 10.82	73.69 ± 10.83	0.490
Body mass index (BMI)	26.8 ± 4.0	28.5 ± 4.6	0.005	27.21 ± 2.86	28.59 ± 3.95	0.006
Diabetes mellitus	34 (20.6%)	42 (82.3%)	0.001	9 (7%)	66 (75.9%)	<0.001
Hyperlipidemia	63 (38.1%)	32 (62.7%)	0.002	51 (39.5%)	45 (51.7%)	0.052
Hypertension	102 (61.8%)	35 (68.6%)	0.331	84 (65.1%)	54 (62.1%)	0.376
Cardiopulmonary bypass time (min)	83.6 ± 22.8	97.5 ± 54.0	0.079	82.65 ± 25.34	93.07 ± 41.92	0.024
Aorta cross clamp time (min)	51.0 ± 18.1	57.2 ± 23.9	0.092	49.72 ± 18.53	56.62 ± 20.85	0.011
Drug history						
ACE I	117 (70.9%)	36 (70.5%)	1.000	78 (60.5%)	75 (86.2%)	<0.001
Angiotensin 2 blocker	24 (14.5%)	21 (41.1%)	0.001	21 (16.3%)	24 (27.6%)	0.034
Beta blockers	135 (81.8%)	31 (60.7%)	0.001	96 (74.4%)	69 (79.3%)	0.254
Calcium channel blockers	28 (16.9%)	27 (52.9%)	0.001	21 (16.3%)	33 (37.9%)	<0.001
Diuretics	30 (18.1%)	24 (47.0%)	0.001	15 (11.6%)	39 (44.8%)	<0.001
Glibenclamide	31 (18.7%)	32 (62.7%)	0.001	6 (4.7%)	57 (65.5%)	<0.001
Metformin	20 (12.1%)	24 (47.0%)	0.001	3 (2.3%	42 (48.3%)	<0.001
Insulin NPH	18 (10.9%)	14 (27.4%)	0.003	3 (2.3%)	30 (34.5%)	<0.001
Insulin regular	18 (10.9%)	17 (33.3%)	0.001	3 (2.3%)	33 (37.9%)	<0.001
Angiography results						
LM lesion	20 (12.1%)	18 (35.2%)	0.001	9 (7%)	30 (34.5%)	<0.001
LAD lesion	162 (98.1%)	51 (100%)	1.000	129 (100%)	84 (96.6%)	0.064
RCA lesion	129 (78.1%)	42 (82.3%)	0.657	102 (79.1%)	69 (79.3%)	0.553
LCX lesion	102 (61.8%)	30 (58.8%)	0.827	84 (65.1%)	48 (55.2%)	0.092

HbA1C: hemoglobin A1C; FBS: fasting blood sugar; LM: left main; LAD: left anterior descending; RCA: right coronary artery; LCX: left circumflex artery

Table 2 Comparing postoperative complications based on HbA1C and FBS levels

Complications	A1cHb ≤7 (n = 165)	A1cHb >7 (n = 51)	p	FBS ≤126 mg/dl (n = 129)	FBS >126 mg/dl (n = 87)	p
Arrhythmia	45 (27.2)	20 (39.2)	0.087	26 (20.1%)	37 (42.5%)	0.001
Myocardial infarction	3 (1.8%)	1 (1.9%)	1.000	3 (2.3%)	1 (1.1%)	0.401
Congestive heart failure (CHF)	1 (0.6%)	4 (7.8%)	0.003	0	3 (3.4%)	0.064
Tamponade	14 (8.4%)	4 (7.8%)	0.574	4 (3.1%)	3 (3.4%)	0.622
Intra-aortic balloon pump	4 (2.4%)	8 (15.6%)	0.001	0	2	0.161
Respiratory						
Atelectasis	58 (35.1%)	17 (33.3%)	1.000	39 (30.2%)	38 (43.6%)	0.029
Lung infection	1 (0.6%)	3 (5.8%)	0.410	1 (0.7%)	3 (3.4%)	0.61
Re-intubation	7 (4.2%)	11 (21.5%)	0.001	7 (5.4%)	11 (12.6%)	0.027
Mechanical ventilation time (hr)	13.0 (8.0–17.0)	14.0 (9.0–17.0)	0.238	10 (7–15)	15 (12–20%)	0.001
ICU stay (day)	4.0 (3.0–4.0)	4.0 (3.0–5.0)	0.430	4 (3–4)	4 (3–5)	0.065
Others						
Sepsis	1 (0.6%)	3 (5.8%)	0.042	0	3 (3.4%)	0.064
Wound infection	4 (2.4%)	8 (15.6%)	0.001	1 (0.7%)	11 (12.6%)	0.001
Renal failure	6 (3.6%)	3 (5.8%)	0.445	3 (2.3%)	6 (6.8%)	0.099
Excessive bleeding (>1000 cc/24h)	32 (19.3%)	18 (35.2%)	0.039	30 (23.2%)	21 (24.1%)	0.881
Bedsore	4 (2.4%)	3 (5.8%)	1.000	4 (3.1%)	3 (3.4%)	0.622
Multi organ failure(MOF)	0	3 (5.8%)	0.013	0	2 (2.2%)	0.161
Death	4 (2.39%)	2 (3.92%)	0.628	3 (2.31%)	2 (2.33%)	1.000

HbA1C: hemoglobin A1C; FBS: fasting blood sugar; ICU: intensive care unit

Table 3 Binary logistic regression analysis for association between postoperative complications and HbA1c >7

Covariates	Relative risk	95% Confidence interval	p
Re-intubation	8.15	2.88–23.09	0.001
Wound infection	11.57	3.00–44.64	0.001
Postop. bleeding	2.18	1.10–4.35	0.027

Table 4 Binary logistic regression analysis for association between postoperative complications and FBS >126 mg/dL

Covariates	Relative risk	95% Confidence interval	p
Arrhythmia	3.07	1.69–5.59	0.001
Atelectasis	1.88	1.07–3.30	0.029
Wound infection	8.75	2.45–31.25	0.001

mortality or morbidity rates after CABG. It has previously been proven that patients with higher glucose also suffer worse outcomes.[1–3] On the other hand, several studies in past years have found that higher HbA1c levels lead to adverse outcomes in patients.[8–12] The present study found that preoperative FBS levels have higher association with arrhythmia, atelectasis and prolonged mechanical ventilation while preoperative HbA1C levels are of higher association with IABP, massive bleeding (>1000 mL/24h) and multi-organ failure.

Former studies suggest that preoperative higher blood glucose levels raise the risk of infection and tighten inflammatory responses.[3,13,14] We found a significant relationship between sepsis, wound infection with high levels of both HbA1c and FBS in univariate and multivariate analyses.

In many studies, the relationship between numerous postoperative complications after CABG and high FBS[15] or high HbA1C[2,10] have been evaluated. Previously, it was shown that high HbA1c levels are associated with an increased risk of postoperative wound infections and sepsis.[7] Another study demonstrated that hyperglycemia increases the rate of postoperative infections both in adult[14] and pediatric patients.[16] It seems that reactive oxygen species (ROS) formation is involved in this issue.[8] Hyperglycemia promotes intravascular formation of ROS which in turns might accelerate myocardial oxidative damage and develop or intensify infection.[3,8] This mechanism also plays an important role in cellular damage due to CHF and also respiratory complications such as pulmonary infection and atelectasis.[10]

Increased incidence of postoperative arrhythmias and myocardial infarction has been suggested in patients with high levels of blood sugar.[17,18] Halkos et al. studied the association of multiple outcomes with elevated HbA1c levels and showed that HbA1c as a glucose control index during the preceding 3 to 4 months is a powerful predictor of in-hospital mortality and morbidity.[6]

Similar to the study of Knapik and colleagues,[7] our study showed that preoperative glycemic control had no significant association with mortality. They found that higher incidence rate of perioperative myocardial infarction in diabetic patients had a strong association with elevated HbA1c levels. This finding is similar to the study of Halkos, et al.[6] as in their study, each unit increase in HbA1c level was associated with a significantly increased risk of myocardial infarction and also deep sternal wound infection. However, in our study we did not find any strong association between myocardial infarction and high levels of FBS or HbA1c.

Conclusions

Considering the fact that abundant similar studies have not been performed so far, this study definitely and firmly does not indicate that which one- either high HbA1C or acute preoperative hyperglycemia has a better association with postoperative adverse events. Nevertheless, both of these indexes certainly raise the risk of postoperative complications but not the mortality rates.

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Disclosure Statement

The authors declare no conflict of interest in this study.

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