Relationship Between Elevated HbA1c and Deep Sternal Wound Infection in Patients Undergoing Cardiac Surgery

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ABSTRACT

Introduction: Hyperglycemia is common in patients with and without diabetes mellitus (DM) following cardiac surgery. Intra- and postoperative hyperglycemia has been shown to be an independent risk factor for deep sternal wound infection (DSWI) after cardiac surgery. However, whether the preoperative chronic glycemic control is associated with the risk of DSWI remains controversial. Hemoglobin A1c (HbA1c) provides a measure of glucose control over the prior 2-3 months. The aim of this study was to evaluate the relationship between preoperative HbA1c levels and DSWI in patients with DM undergoing coronary artery bypass grafting (CABG).

Patients and Methods: Records of patients who underwent elective on-pump CABG were retrospectively reviewed. A total of 180 patients with DM were included in the study. Patients were excluded if their blood glucose levels were not adequately controlled in the perioperative period. A total of 200 consecutive patients without DM were taken as controls.

Results: Median HbA1c levels were significantly higher in patients with DM [8.16 (7.2-10.4)] than in controls [5.49 (5-6)] (p< 0.001). There was no significant difference in DSWI incidence between patients with DM and controls [5% (n= 9) vs. 2% (n= 4); P= 0.1]. Hospital (p= 0.01) and intensive care unit stays (p= 0.005) were significantly longer in patients with DM.

Conclusion: We found that DSWI was not associated with preoperative HbA1c levels in patients undergoing CABG. In addition, with adequate glycemic control in the perioperative period, our study demonstrated no significant difference with regard to DSWI between patients with DM and controls.

Key Words: Mediastinitis; coronary artery bypass grafting; hemoglobin A1c; diabetes mellitus; deep sternal wound infection

Kalp Cerrahisi Yapılan Hastalarda Derin Sternal Yara İnfeksiyonları ile HbA1c Seviyeleri Arasındaki İlişki

ÖZET

Giriş: Kalp cerrahisi yapılan hastalarda, diabetes mellitus (DM)'lu hastalarda olduğu kadar diyabetik olmayan hastalarda da hiperglisemi ile sık karşılaşılır. Kalp cerrahisi sonrasında intraoperatif ve postoperatif hipergliseminin derin sternal yara infeksiyonu (DSYİ) için bağımsız risk faktörü olduğu gösterilmiştir. Ancak, preoperatif kronik glisemik kontrolün DSYİ ile ilişkisi tartışmalıdır. Hemoglobin A1c (HbA1c) geçmiş 2-3 aylık dönemdeki glukoz düzeyi hakkında bilgi verir. Bu çalışmanın amacı koroner baypas cerrahisi yapılan DM'li hastalarda, HbA1c seviyeleri ile DSYİ arasındaki ilişkiyi incelemektir.

Hastalar ve Yöntem: Kliniğimizde kardiyopulmoner baypas altında koroner baypas operasyonu yapılmış olan hastaların kayıtları retrospektif olarak incelendi. DM'si olan ve perioperatif periyodda yeterli glisemik kontrol sağlanmış 180 hasta çalışmaya dahil edildi. DM'si olmayan koroner baypas cerrahisi yapılmış ardışık 200 hasta kontrol grubuna dahil edildi.

Bulgular: Medyan HbA1c değerleri diyabetik hasta grubunda anlamlı olarak daha yüksekti [8.16 (7.2-10.4 vs 5.49 (5-6), p < 0.001]. DSYİ sıklığı bakımdan iki grup arasında istatistiksel olarak anlamlı bir fark saptanmadı [%5 (n= 9) vs %2 (n= 4); p= 0.1]. Yoğun bakımda kalış (p= 0.005) ve hastanede kalış süreleri (p= 0.01) diyabetik hastalarda anlamlı olarak daha uzundu.

Sonuç: Preoperatif dönemdeki yüksek HbA1c seviyeleri koroner baypas sonrası DSYİ ile ilişkili bulunmamıştır. Ayrıca perioperatif periyodda yeterli glisemik kontrol sağlanmış DM'li hastalarda DSYİ sıklığında artış olmadığı saptanmıştır.

Anahtar Kelimeler: Mediastinit; koroner arter baypas cerrahisi; hemoglobin A1c; diabetes mellitus, derin sternal yara infeksiyonu



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INTRODUCTION

The incidence of deep sternal wound infections (DSWIs) is between 0.4 and 5% following cardiac surgery and is associated with significant perioperative morbidity and mortality⁽¹⁻⁴⁾. The associated mortality is reported to be as high as 47%⁽⁵⁾. The etiology of DSWI is multifactorial. Previous studies have reported several factors associated with the risk of DSWI⁽⁶⁻⁸⁾.

Hyperglycemia is common in patients with and without diabetes mellitus (DM) following cardiac surgery $^{(9,10)}$. Intra- and postoperative hyperglycemia has been shown to be an independent risk factor for infections⁽¹¹⁻¹³⁾. Previous studies demonstrated that intra and postoperative glycemic control improves the risk of infections following cardiac surgery^(2,12-15). However, whether the preoperative chronic glycemic control is associated with the risk of infections remains controversial. Furthermore, it is currently unclear whether patients with poor chronic glucose control have their surgery delayed to minimize perioperative complications. Glycosylated hemoglobin (hemoglobin A1c, HbA1c) is a sensitive and reliable biomarker that provides a measure of glucose control over the prior months (2-3). The American Diabetes Association suggests an HbA1c goal of 7% or lower to reduce the long-term complications of $DM^{(16,17)}$.

The aim of this study was to evaluate the association between preoperative chronic glycemic state (using the surrogate HbA1c laboratory value) and DSWI after coronary artery bypass grafting (CABG) in patients with DM.

PATIENTS and METHODS

Study Population

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Records of the patients who underwent primary elective CABG using cardiopulmonary bypass (CPB) between January 2009 and December 2014 were retrospectively reviewed. Inclusion criteria consisted patients with DM who had a documented preoperative HbA1c within 1 month before surgery.

Exclusion criteria were as follows: (1) a preoperative blood hemoglobin concentration of < 9 mg/dL, (2) emergency procedures, (3) redo CABG, (4) off pump CABG, (5) patients without a mammary artery graft, (6) patients with poor perioperative glycemic control, (7) missing preoperative HbA1c data, and (8) patients missing postoperative controls. Patients with a blood hemoglobin concentration of < 9 mg/dL were excluded because of the possible confounding effect of anemia on HbA1c. Patients with poor perioperative glycemic control were excluded to reduce the confounding effect of perioperative BG levels on the analysis.

After applying the inclusion and exclusion criteria, 180 patients with DM were included in the study. A total of 200

consecutive patients without DM who underwent elective CABG were taken as controls. DM was defined as having a fasting plasma glucose level of ≥ 126 mg/dL or treatment with insulin or a hypoglycemic agent. Hypertension (HT) was defined as a systolic blood pressure of > 140 mmHg, diastolic blood pressure of > 90 mmHg, or use of an antihypertensive medication. Hyperlipidemia (HL) was defined as a total serum cholesterol (TC) of ≥ 200 mg/dL, low density lipoprotein cholesterol (LDL) of ≥ 130 mg/dL, triglycerides (TG) of ≥ 200 mg/dL, and/or history of the use of lipid-lowering regiment.

Surgical Technique

All procedures were performed using median sternotomy under general anesthesia. Standard nonpulsatile CPB with a roller pump (stroker) and a membrane oxygenator was used. Intermittent antegrade blood cardioplegia and systemic hypothermia (28°C) were used. The left internal mammary artery (LIMA) was used for surgical revascularization of the left anterior descending artery in all cases. LIMA was harvested as pedicle grafts in all patients. We minimized the use of bone wax.

Standardized protocols for bathing, *Staphylococcus* decolonization, perioperative glucose management, and antimicrobial prophylaxis were used. Cefazolin was administered to nonpenicillin-allergic patients and vancomycin to penicillin-allergic patients. Prophylactic antibiotics were initiated within 1 h before surgical incision or within 2 h if the patient was receiving vancomycin and was continued for 48 h. We followed the same perioperative infection control in all cases.

Deep Sternal Wound Infection

DSWI was defined according to the Society of Thoracic Surgeons National Database criteria: a sternal infection involving the muscle, bone, pericardium, and/or mediastinum within 30 days postoperatively that requires 6 weeks of antibiotics with or without operative intervention. In addition, the diagnosis of postoperative mediastinitis was based on the guidelines of the Center for Disease Control and Prevention, using at least one of the following criteria: bacteria isolated from cultures of mediastinal tissues or fluid, evidence of mediastinitis during surgery, or one of the following conditions: chest pain, sternal instability, or fever (> 38°C), in combination with purulent discharge from the mediastinal drainage⁽¹⁸⁾. DSWI cases were identified with the assistance of a hospital infection control team. We followed the same perioperative infection control in all cases.

Blood Glucose Management

The measurement of HbA1c is a routine part of the preoperative evaluation in patients with DM in our clinic. All patients with DM received endocrinology consultation for better control in the pre and postoperative period. Oral antidiabetic agents were stopped prior to surgery in all patients. Patients received no diabetic medicines on the morning of surgery. In the preoperative period, insulin therapy was started for the blood glucose level of > 200 mg/dL and adjusted to maintain

a blood glucose level of < 200 mg/dL. Blood glucose was monitored every 4-6 h. Intraoperatively, glucose levels were measured approximately every hour, and continuous insulin infusions were started if glucose level was > 200 mg/dL. All patients received continuous insulin infusion in the operating room and for at least 24 h postoperatively to maintain serum glucose levels of < 200 mg/dL. Insulin infusions were usually discontinued, and the patients converted to subcutaneous insulin on the morning of postoperative day 1. All patients were discharged on multiple daily insulin therapy.

Statistical Analysis

Statistical analysis was conducted using SPSS for Windows version 17 (SPSS, Chicago, IL, USA). All variables were investigated using visual (histograms and probability plots) and analytic methods (Kolmogorov-Smirnov test) to determine whether or not they were normally distributed. Continuous variables were reported as means and standard deviation for normally distributed variables and as medians and interquartile range for the non-normally distributed variables. Categorical variables were presented using numbers and percentages.

Comparison between patients with DM and controls was performed using the chi-square test for qualitative variables, independent t test for normally distributed continuous variables, and Mann-Whitney U test for non-normally distributed continuous variables. Post-hoc power of the study was 0.77. Statistical significance was defined as p< 0.05.

RESULTS

Clinical and biochemical characteristics of patients with DM (n= 180; 101 males; mean age \pm SD, 62.5 \pm 10.3) and controls (n= 200; 103 males; mean age \pm SD, 57.8 \pm 11.06) are presented in Table 1. Patients with DM were significantly older than controls (p< 0.001). Incidences of HT (p= 0.005) and COPD (p= 0.02) were significantly higher in patients with DM than in controls. Hospital (p= 0.01) and intensive care unit (ICU) stays (p= 0.005) were significantly longer in patients with DM. HL incidence was significantly higher in controls than in patients with DM (p= 0.004). HbA1c levels were significantly higher in patients with DM than in controls with DM than in controls (p< 0.001). There were no statistically significant differences in other clinical

	DM group (n= 180)	Control group (n= 200)	р
Age, years, mean ± SD	62.5 ± 10.3	57.8 ± 11.06	< 0.001
Gender, male, n (%)	101 (56.1)	103 (51.5)	0.36
HL, n (%)	54 (30)	89 (44.5)	0.004
HT, n (%)	135 (75)	123 (61.5)	0.005
COPD, n (%)	81 (45)	66 (33)	0.02
Smoking, n (%)	94 (52.2)	99 (49.5)	0.6
Obesity, n (%)	45 (25)	59 (29.5)	0.3
BMI, kg/m ² , mean \pm SD	28.2 ± 2.4	28.2 ± 2.9	0.96
HbA1C, median (IQR)	8.16 (7.2-10.4)	5.49 (5-6)	< 0.001
EF, %,	49.3 ± 8.9	50.2 ± 8.8	0.32
Emergency operation, n (%)	13 (7.2)	16 (8)	0.8
Anastomoses, mean \pm SD	3.68 ± 1.03	3.7 ± 0.99	0.83
CPB time, min, median (IQR)	99 (86-113.7)	101 (81.2-113)	0.76
X clamp time, min, mean \pm SD	64.9 ± 19.4	65.4 ± 18.1	0.8
Number of transfusions, mean ± SD	2.76 ± 1.74	2.59 ± 1.76	0.34
Bleeding, 24 h, mean ± SD	685.5 ± 516.3	643.2 ± 455.5	0.4
Re-exploration for bleeding, n (%)	12 (6.7)	11 (5.5)	0.63
LCOS, n (%)	14 (7.8)	10 (5)	0.26
IABP, n (%)	5 (2.8)	4 (2)	0.7
Ventilation time, h, mean \pm SD	9.3 ± 4.1	8.5 ± 4.6	0.07
Postoperative renal failure, n (%)	2 (1.1)	3 (1.5)	0.7
DSWI, n (%)	9 (5)	4 (2)	0.1
ICU stay, days, median (IQR)	1 (1-2)	1 (1-1)	0.005
Hospital stay, days, median (IQR)	6.5 (6-8)	6 (5-7)	0.01

Table 1 Differences in clinical and high-micel characteristics of the notion to consuding to the presence of dichetes multitude

p: p values for between group comparisons; BMI: Body mass index; HT: Hypertension; HL: Hyperlipidemia; COPD: Chronic obstructive pulmonary disease; DSWI: Deep sternal wound infection; Hct: Hematocrit; CPB: Cardiopulmonary bypass; ScVO2: Central venous oxygen saturation; IABP: Intra-aortic balloon pump; LCOS: Low cardiac output syndrome; ICU: Intensive care unit.

characteristics listed in Table 1 between the two groups. There was no significant difference between patients with DM and controls with regard to DSWI (5% vs. 2%, p= 0.1).

DISCUSSION

We found that DSWI was not associated with preoperative HbA1c levels in patients undergoing CABG. In addition, with adequate glycemic control in the perioperative period, our study demonstrated no significant difference with regard to DSWI between patients with DM and controls.

Previous studies showed controversial results regarding the relationship between DM and DSWI following cardiac surgery. Some previous studies support our results. Milano et al. conducted a study to determine pre and intraoperative variables that predict DSWI. DM was shown to be a predictor using univariate analysis. However, DM was not a predictor of mediastinitis using multivariate analysis⁽⁶⁾. Similar results were obtained by Loop et al. who studied wound complications in 6.504 patients undergoing isolated CABG. They found that DM was not a predictor of mediastinitis using multivariate analysis⁽¹⁹⁾ Trick et al. conducted a study to identify the risk factors for DSWI after CABG⁽²⁰⁾. They demonstrated that diabetes was a risk factor only when the preoperative blood glucose level was ≥ 200 mg/dL. On the other hand, Nagachinta et al. investigated the risk factors for surgical wound infection following CABG in 1.009 patients⁽²¹⁾. DM was found to be an independent risk factor for sternal or mediastinal wound infection. Risnes et al. examined the risk factors of mediastinitis in 18.532 patients who underwent CABG⁽⁵⁾. They showed that DM was an independent risk factor for DSWI. Badawy et al. investigated the risk factors for mediastinitis in 1.424 patients undergoing isolated CABG⁽²²⁾. DM was shown to be an independent risk factor for DSWI. However, perioperative glycemic control was not taken into account as a confounding variable in these studies. It should be pointed out that in our study, patients with poor perioperative blood glucose control were excluded to eliminate the confounding influence of perioperative blood glucose levels.

It is still unclear whether there is an association between HbA1c levels and DSWI after cardiac surgery. Engoren et al. investigated the effect of HbA1c on complications in 880 patients undergoing CABG who were managed with tight postoperative glycemic control⁽²³⁾. No relationship was found between HbA1c and sternal wound infections. In addition, they found no relationship between DM and postoperative complications. Knapik et al. examined the relationship between HbA1c and postoperative outcomes in 735 patients undergoing CABG with tight postoperative glycemic control, and elevated HbA1c levels were not associated with wound infections⁽²⁴⁾. Matsuura et al. evaluated the postoperative outcome of the OPCAB in patients with poorly controlled DM (HbA1c > 6.5) ⁽²⁵⁾. Wound infection was not related to HbA1c levels. Hudson et al. examined the relationship between HbA1c and outcomes in 1.474 nondiabetic patients undergoing cardiac surgery⁽²⁶⁾. They found no association between HbA1c and infection after cardiac surgery. Tsuurata et al. also studied the impact of HbA1c levels on the outcomes of patients with DM after off-pump CABG⁽²⁷⁾. No relationship was found between HbA1c and DSWI. Latham et al. assessed the role of preoperative chronic glucose control in the development of surgical site infections⁽²⁸⁾. Increased risk of infection was not associated with HbA1c (HbA1c > 8%) in the preoperative period. They found DM and postoperative blood glucose levels to be an independent risk factor for surgical site infection. Alserius et al. investigated the relationship between HbA1c levels and postoperative infections⁽²⁹⁾. Although not statistically significant, DSWI incidence was higher in patients who had an HbA1c level of $\geq 6\%$. They demonstrated that HbA1c was associated with a significantly increased risk of superficial sternal wound infections. Our findings are contradictory to those of some reports. Fohl et al. examined the relationship between HbA1c and DSWI in 861 cardiac surgery patients with DM whose postoperative blood glucose was maintained between 100-140 mg/dL⁽³⁰⁾. Preoperative HbA1c levels of > 8.5 was found to be associated with an increased incidence of DSWI. Faritous et al. evaluated whether HbA1C could predict probable adverse events after CABG in 216 patients⁽³¹⁾. They showed a significant relationship between high levels of HbA1c (HbA1c > 7) and wound infection. However, a detailed evaluation of the association between HbA1c and DSWI was not performed. Halkos et al. evaluated the relationship between HbA1c and adverse outcomes following CABG⁽³²⁾. They found that an HbA1c levels of > 7.8% was associated with a 5 fold increase in DSWI.

In the present study, no significant difference with regard to DSWI was found between patients with DM and controls. This may be related to the fact that patients had adequate glycemic control in the perioperative period. Additionally, hospital and ICU stays were longer in patients with DM than in controls. This may be related to the higher frequency of COPD in patients with DM.

Limitations

Our study has the following limitations. First, this is a singlecenter retrospective study. Second, we have not evaluated the relationship between HbA1c levels and postoperative complications.

CONCLUSION

Our results indicate that poor chronic glucose control (as reflected by the elevated HbA1c levels) in the preoperative period is not a risk factor for DSWI in patients undergoing CABG. Additional prospective multicenter clinical studies that involved a large number of patients are needed to confirm our results.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Desing: US, AB Analysis/interpretation: US, AB, BY Data acquisition: NA, AB, EB, RA, SA, AE, UB, VA Writing: US Critical revision: NA Final approval: All of authors

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