World J Surg (2017) 41:200–207
DOI 10.1007/s00268-016-3763-z

ORIGINAL SCIENTIFIC REPORT

Preoperative Glycosylated Hemoglobin Levels Predict Anastomotic Leak After Esophagectomy with Cervical Esophagogastric Anastomosis

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Published online: 11 October 2016

Abstract

Background Patients with diabetes are considered at increased risk of delayed wound healing and infectious complications, yet the relationship between diabetes and anastomotic leak (AL) remains unclear. Given that glycosylated hemoglobin (HbA1c) is a validated indicator of the long-term glycemic state, we evaluated the relationship between preoperative HbA1c levels and AL after esophagectomy.

Methods We assessed 300 consecutive patients who underwent esophagectomy reconstructed with cervical esophagogastric anastomosis between 2011 and 2015. HbA1c levels were measured within 90 days before esophagectomy. We performed comparison between the patients with and without diabetes. In addition, the predictive factors for AL, as well as the relationship between HbA1c levels and AL, were investigated.

Results Among the 300 patients, 35 had diabetes. The overall prevalence of AL was 11.7%, and patients with diabetes had a higher prevalence of AL than those without ($p = 0.045$). In univariate analysis, we identified diabetes, HbA1c level, and hand-sewn anastomosis as risk factors for AL significantly ($p = 0.033$, 0.009, and 0.011, respectively), but we also found previous smoking history, chronic hepatic disease, and supracarinal tumor location also showed tendencies to be risk factors ($p = 0.057$, 0.055, and 0.064, respectively). Multivariate logistic regression analysis indicated that chronic hepatic disease ($p = 0.048$), increased HbA1c level ($p = 0.011$), and hand-sewn anastomosis ($p = 0.021$) were independent risk factors for AL.

Conclusions Preoperative HbA1c level was significantly associated with the development of AL after cervical esophagogastric anastomosis. We recommend preoperative HbA1c screening for all patients scheduled to undergo esophagectomy.

Introduction

Anastomotic leak (AL) after esophagectomy is an important cause of both postoperative mortality and prolonged hospitalization [1]. Furthermore, a large multicenter study recently suggested that severe AL could correlate with poor long-term survival [2]. According to nationwide databases, AL has been reported to occur in 10.1–13.3 % of patients [2–4]. Thus, several studies have been published to identify risk factors for the development of AL after esophagectomy [1, 5–12].

Generally, diabetic patients are considered to have an increased risk of postoperative complications, especially infection and delayed wound healing [13–15]. However, the relationship between diabetes and AL in patients undergoing esophagectomy remains unclear. In a previous study, it was reported that diabetes was significantly associated with major AL after intrathoracic esophagogastric anastomosis

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[10]. Meanwhile, another study revealed that diabetes was not an independent predictor of cervical esophagogastric AL [16]. However, the diagnosis of diabetes in these previous studies was based on clinical history, so there is uncertainty because of the possibility of undiagnosed diabetes influencing the results.

Glycosylated hemoglobin (HbA1c) is a validated indicator used to assess long-term glycemic control among patients with diabetes, with levels having been shown to reflect how well diabetes is controlled [17]. The HbA1c test is also used as a screening for diabetes. Recently, several studies have revealed a relationship between preoperative HbA1c levels and surgical outcomes after cardiac, orthopedic, gynecologic, and major abdominal surgeries [18–22]. However, no studies have reported the effect of HbA1c levels on complications after esophagectomy, and specifically of AL.

In this study, we aimed to evaluate whether the HbA1c level was a useful predictor of AL after cervical esophagogastric anastomosis.

Material and methods

Patients

We retrospectively included 300 consecutive patients who underwent subtotal esophagectomy reconstructed with cervical esophagogastric anastomosis through a retrosternal or posterior mediastinal route for esophageal cancer. The study was performed at The Cancer Institute Hospital of Japanese Foundation for Cancer Research, between 2011 and 2015. We reviewed medical records and collected data for patients' characteristics and surgical outcomes. Tumor stage was classified according to the Union for International Cancer Control [23]. The study protocol was approved by our institutional review board.

Measurement of HbA1c and definition of diabetes

During preoperative evaluation, HbA1c levels were measured within 90 days before surgery in all patients, as the ratio between the glycosylated hemoglobin and total hemoglobin levels, and were given as a percentage according to the National Glycohemoglobin Standardization Program unit. In this study, patients were defined as having diabetes if they had a previous diagnosis of diabetes, had received therapy for diabetes before the preoperative evaluation, or had no prior diagnosis but a preoperative HbA1c $\geq$6.5 %.

Perioperative glycemic management of patients with diabetes

Perioperative glycemic management was optimized on the basis of recommendations from a diabetologist. If time allowed and the glycemic control was poor, additional attempts were made to improve glycemic control preoperatively. The goal of intervention was to achieve a fasting blood glucose $<$140 mg/dL and no urinary excretion of ketone bodies. After surgery, patients with diabetes and a blood glucose $\geq$200 mg/dL received continuous intravenous insulin by infusion to maintain glucose levels $<$200 mg/dL. Non-diabetic patients received insulin injections on a conventional sliding scale to achieve a target glucose of $<$200 mg/dL.

Preoperative chemotherapy or chemoradiotherapy

After diagnosis of esophageal cancer, a treatment plan was decided for each patient according to the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus produced by The Japan Esophageal Society [24]. Principally, no preoperative treatment was performed for patients with clinical stage (cStage) I disease, while neoadjuvant chemotherapy was performed for patients with cStage II/III disease, excepting T4 tumors. Chemoradiotherapy was performed for patients with T4 tumors or who opted for definitive chemoradiotherapy regardless of the tumor stage. If chemoradiotherapy failed to achieve locoregional disease control, salvage surgery was recommended.

Surgical procedure and anastomotic technique

All patients underwent radical esophagectomy with lymph node dissection via the cervico-thoraco-abdominal approach. The thoracic procedure was performed from the right thorax using either a thoracoscopic approach in the prone position or open transthoracic approach in the left lateral decubitus position. The esophagus was then dissected along with surrounding fat tissue and lymph nodes. During the cervical procedure, paraesophageal and supraclavicular lymph node dissection was performed after considering the condition of the patient and tumor factors.

For the abdominal procedure, gastric mobilization with preservation of the right gastroepiploic vessels and dissection of the abdominal lymph nodes was performed using either a laparoscopic or open abdominal approach. A gastric conduit was then created to a width of 3.5–4 cm using a linear stapler along the greater curvature of the stomach. No pyloric drainage procedure was performed. After the conduit was delivered through the retrosternal or posterior mediastinal route, esophagogastric anastomosis was

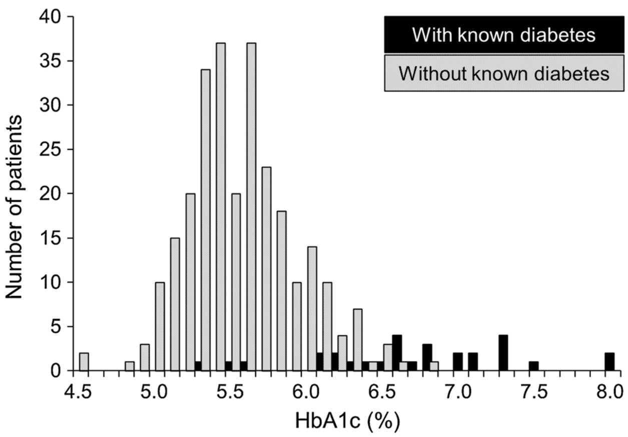

Fig. 1 Distribution of HbA1c levels among patients with and without a previous diagnosis of diabetes. *HbA1c* glycosylated hemoglobin

performed at the neck. At this point, hand-sewn end-to-end anastomosis was performed, using single- or double-layered running or interrupted absorbable sutures.

From September 2013, however, we mainly performed mechanical anastomosis at the neck, using a previously described triangulating stapling technique [25–27]. This technique was also performed in an end-to-end fashion, applying three staple lines with linear staplers. While creating the gastric conduit, an omental flap pedicle was also prepared (i.e., omentoplasty) and carefully brought up to the neck with the conduit. Finally, the anastomotic site was wrapped by the flap.

Definition of AL

AL was defined as follows: (1) the presence of clinical signs of AL, such as skin edema, redness, or the emission of residual saliva, pus, or food from the cervical wound or drain; and/or (2) the presence of confirmed radiological signs of AL, such as leaking of contrast medium from the anastomotic site on an esophagogram, or evidence of abscess formation around the anastomotic site on computed tomography.

Statistical analysis

All data are presented as the mean ± standard deviation or as number (%). We compared patients' characteristics and surgical outcomes between two populations using the Mann–Whitney *U* test or Fisher's exact test, as appropriate. In addition, we evaluated whether the HbA1c level was associated with AL by univariate and multivariate logistic regression analysis with the HbA1c level as a continuous variable. Multivariate analysis was performed by backward elimination, and odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated. A p value of 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software package (version 22.0; IBM-SPSS, Inc., Chicago, IL, USA).

Results

Prevalence of diabetes and HbA1c distribution among patients with esophageal cancer

Of the 300 patients identified during the study period, 35 (11.7 %) had diabetes. The distribution of HbA1c levels for patients with and without a previous diagnosis of diabetes is shown in Fig. 1. In total, 27 (9.0 %) patients had an HbA1c $\geq$6.5 %, and 6 of the 35 patients with diabetes (17.1 %) had previously undiagnosed disease.

Comparison of patient characteristics and surgical outcomes by diagnosis of diabetes

Patient characteristics and surgical outcomes were compared between patients with and without diabetes (Table 1). Those with diabetes were significantly more likely to be male; to have hypertension, cardiovascular disease, and cerebrovascular disease; and to have higher body mass indexes and higher HbA1c levels than those without ($p = 0.015$, 0.003, 0.005, 0.045, 0.039, and $<$0.001, respectively). In addition, the presence of diabetes was associated with significantly more operative blood loss, more AL, and longer hospital stays after surgery compared with the absence of diabetes ($p = 0.048$, 0.045, and 0.002, respectively). However, no significant differences were found between the two groups with regards age, previous smoking history, other comorbidities, tumor factors, preoperative treatment, surgical procedure, or other postoperative complications.

Risk factors for AL after cervical esophagogastric anastomosis

To determine the risk factors for AL, we performed logistic regression analysis. In the univariate analysis (Table 2), we identified diabetes, HbA1c level, and hand-sewn anastomosis as being significantly predictive for AL ($p = 0.033$, 0.009, and 0.011, respectively), but we also found previous smoking history ($p = 0.057$), chronic hepatic disease ($p = 0.055$), and supracarinal tumor location ($p = 0.064$) also showed tendencies to be risk factors. Of all main variables, chronic hepatic disease (OR 3.72, 95 % CI 1.01–13.7, $p = 0.048$), HbA1c level (OR 2.17, 95 % CI 1.19–3.93, $p = 0.011$), and hand-sewn anastomosis (OR 2.44, 95 % CI 1.14–5.23, $p = 0.021$) remained

Table 1 Patient characteristics and surgical outcomes

Variables	Total ($n = 300$)	Patients without diabetes ($n = 265$)	Patients with diabetes ($n = 35$)	p value
Age (years)	63 ± 8	63 ± 8	65 ± 7	0.366
Gender				0.015*
Male	250 (83.3)	216 (81.5)	34 (97.2)	
Female	50 (16.7)	49 (18.5)	1 (2.8)	
Body mass index (kg/m^2)	21.9 ± 3.0	21.7 ± 2.9	23.4 ± 3.3	0.003*
Previous smoking	245 (81.7)	215 (81.1)	30 (85.7)	0.645
Previous medical history				
Hypertension	120 (40.0)	98 (37.0)	22 (62.9)	0.005*
Cardiovascular disease	18 (6.0)	13 (4.9)	5 (14.3)	0.045*
Cerebrovascular disease	12 (4.0)	8 (3.0)	4 (11.4)	0.039*
Chronic liver disease	14 (4.7)	12 (4.0)	2 (5.7)	0.671
Obstructive lung disease	77 (25.7)	69 (26.0)	8 (22.9)	0.838
Laboratory findings				
Albumin (mg/dl)	4.1 ± 0.3	4.1 ± 0.2	4.2 ± 0.3	0.813
HbA1c (%)	5.7 ± 0.5	5.6 ± 0.3	6.7 ± 0.6	<0.001*
Histological type				0.519
Squamous cell carcinoma	269 (89.7)	239 (90.2)	30 (85.7)	
Adenocarcinoma	27 (9.0)	22 (8.3)	5 (14.3)	
Others	4 (1.3)	4 (1.5)	0 (0.0)	
Preoperative treatment				0.515
None/endoscopic resection	122 (40.7)	106 (40.0)	16 (45.7)	
Chemotherapy	159 (53.0)	143 (54.0)	16 (45.7)	
Chemoradiotherapy	19 (6.3)	16 (6.0)	3 (8.6)	
Main tumor location				1.000
Supracarinal	73 (24.3)	65 (24.5)	8 (22.9)	
Infracarinal	227 (75.7)	200 (75.5)	27 (77.1)	
pT category				0.859
pT ≤ 1b	167 (55.7)	148 (55.8)	19 (54.3)	
pT ≤ 1b	133 (44.3)	117 (44.2)	16 (45.7)	
pN category				0.473
pN0	157 (52.3)	141 (53.2)	16 (45.7)	
pN ≥ 1	143 (47.7)	124 (46.8)	19 (54.3)	
pStage category				0.851
pStage ≤ II	199 (66.3)	175 (66.0)	24 (68.6)	
pStage ≥ III	101 (33.7)	90 (34.0)	11 (31.4)	
Thoracic approach				1.000
Thoracoscopic	227 (75.7)	200 (75.5)	27 (77.1)	
Open thoracic	73 (24.3)	65 (24.5)	8 (22.9)	
Abdominal approach				0.104
Laparoscopic	135 (45.0)	124 (46.8)	11 (31.4)	
Open abdominal	165 (55.0)	141 (53.2)	24 (68.6)	
Route of reconstruction				0.071
Retrosternal	157 (52.3)	144 (54.3)	13 (37.1)	
Posterior mediastinal	143 (47.7)	121 (45.7)	22 (62.9)	
Extent of lymph node dissection				0.354
Three-field	187 (62.3)	168 (63.4)	19 (54.3)	
Two-field or less	113 (37.7)	97 (36.6)	16 (45.7)	
Anastomotic method				0.280

Table 1 continued

Variables	Total ($n = 300$)	Patients without diabetes ($n = 265$)	Patients with diabetes ($n = 35$)	p value
Hand-sewn	135 (45.0)	116 (43.8)	19 (54.3)	
Linear stapled	165 (55.0)	149 (56.2)	16 (45.7)	
Operative time (min)	596 ± 88	593 ± 86	620 ± 102	0.228
Operative blood loss (mL)	298 ± 260	291 ± 261	353 ± 246	0.048*
Postoperative complications				
Pneumonia	79 (26.3)	66 (24.9)	13 (37.1)	0.152
Anastomotic leak	35 (11.7)	27 (10.2)	8 (22.9)	0.045*
Recurrent laryngeal nerve palsy	78 (26.0)	66 (24.9)	12 (34.3)	0.304
Other surgical site infection	26 (8.7)	22 (8.3)	4 (11.4)	0.523
Length of stay after surgery (days)	29 ± 36	28 ± 37	35 ± 23	0.002*

Data are presented as mean ± standard deviation or n (%)

HbA1c glycosylated hemoglobin

* $p < 0.05$

Table 2 Univariate analysis for factors predicting anastomotic leak

Variables	Odds ratio (95% CI)	p value
Age	0.99 (0.95–1.03)	0.744
Male	2.30 (0.67–7.82)	0.183
Body mass index (kg/m^2)	1.08 (0.96–1.21)	0.190
Previous smoking	4.12 (0.95–17.7)	0.057†
Comorbidities		
Hypertension	1.00 (0.48–2.05)	1.000
Diabetes	2.61 (1.08–6.32)	0.033*
Cardiovascular disease	1.56 (0.42–5.69)	0.499
Cerebrovascular disease	1.54 (0.32–7.36)	0.585
Chronic hepatic disease	3.29 (0.97–11.1)	0.055†
Obstructive lung disease	1.00 (0.44–2.24)	0.995
Laboratory findings		
Albumin (mg/dl)	1.68 (0.57–4.95)	0.345
HbA1c (%)	2.14 (1.21–3.79)	0.009*
Squamous cell carcinoma	0.87 (0.28–2.68)	0.821
Preoperative chemoradiotherapy	2.15 (0.67–6.89)	0.197
Main tumor located in supracarina	2.01 (0.96–4.24)	0.064†
pT ≥ 2	1.06 (0.52–2.16)	0.861
pN ≥ 1	0.91 (0.45–1.85)	0.806
pStage ≥ III	0.65 (0.29–1.44)	0.292
Thoracoscopic approach	0.78 (0.35–1.71)	0.535
Laparoscopic approach	0.60 (0.28–1.26)	0.179
Three-field lymph node dissection	0.78 (0.38–1.59)	0.501
Posterior mediastinal route	1.53 (0.75–3.13)	0.235
Hand-sewn anastomosis	2.61 (1.25–5.48)	0.011*
Operative time (min)	1.00 (0.99–1.00)	0.250
Operative blood loss (ml)	1.00 (0.99–1.00)	0.309

CI confidence interval *HbA1c* Glycosylated hemoglobin

* $p < 0.05$; $^\dagger p < 0.10$

Table 3 Multivariate analysis for factors predicting anastomotic leak

Variables	Odds ratio (95% CI)	p value
Previous smoking	3.76 (0.86–16.4)	0.079
Chronic hepatic disease	3.72 (1.01–13.7)	0.048*
HbA1c (%)	2.17 (1.19–3.93)	0.011*
Hand-sewn anastomosis	2.44 (1.14–5.23)	0.021*

CI confidence interval *HbA1c* Glycosylated hemoglobin

* $p < 0.05$

independent risk factors for predicting AL after multivariate analysis with backward elimination (Table 3). Previous smoking history also tended to be a risk factor for AL, but remained nonsignificant (OR 3.76, 95 % CI 0.86–16.4, $p = 0.079$).

Rate of AL in the patients stratified by HbA1c levels

To further evaluate the relationship between HbA1c and risk of AL, we compared the incidence of AL by HbA1c level. In total, 223 (74.3 %) patients had an HbA1c <6.0 %, 50 (16.7 %) patients had an HbA1c of 6.0–6.4 %, and 27 (9.0 %) had an HbA1c ≥6.5 %, and the corresponding incidences of AL were 9.6, 12.0, and 29.6 % (Fig. 2). The incidence of AL in patients with an HbA1c ≥6.5 % was significantly higher than that in either of the other groups ($p = 0.014$).

Correlation between the preoperative HbA1c levels and the durations until the healing of AL

Among 35 patients who developed AL, we also evaluated the correlation between the preoperative HbA1c levels and

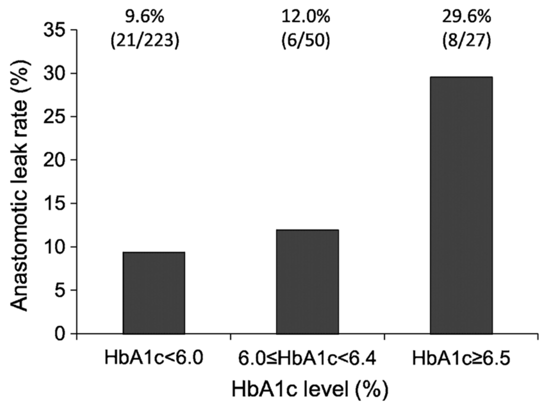

Fig. 2 Rate of anastomotic leak stratified by HbA1c levels. *HbA1c* glycosylated hemoglobin

the durations until the healing of AL. However, there was no significant correlation between them in Spearman's rank correlation coefficient analysis ($r_s = 0.09$, $p = 0.616$).

Discussion

In the present study, we demonstrated the significance of HbA1c levels for predicting the development of AL after cervical esophagogastric anastomosis. This is the first study to indicate the usefulness of preoperative measurement of HbA1c levels in patients undergoing this procedure.

To date, risk factors for AL after esophagectomy have been proposed in several reports. Previously reported predictive factors include smoking, obesity, diabetes, cardiovascular disease, renal insufficiency, chronic hepatic disease, nutritional status, steroid use, anastomotic technique, and the American Society of Anesthesiologists score [1, 5–12]. It was also reported that the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system, which is calculated on the basis of age, various comorbidities (including diabetes), operative blood loss, operative time, and surgical approach, was useful for predicting AL after digestive surgery [8].

Generally, diabetes is clinically considered a risk factor for delayed wound healing as well as surgical infectious complications in several surgical procedures [13–15]. Onodera et al. showed that colonic anastomotic healing was delayed in diabetic rats, with evidence of significantly weakened anastomotic strength when measured by the bursting pressure [28]. In addition, Park et al. showed that diabetic mice were more susceptible to staphylococcal infection than non-diabetic mice, with evidence of persistent infection and impaired neutrophils' function [29].

The pathophysiologic relationship between diabetes and delayed wound healing is complex. Vascular, neuropathic, immune function, and biochemical abnormalities each contribute to the altered tissue repair [30]. In order to overcome the impaired wound healing, additional surgical intervention such as microvascular anastomosis or omentoplasty may be effective [31, 32]. A fluorescent-dye angiography is useful to evaluate perfusion of the gastric conduit intraoperatively and helps surgeons determine the need for vascular enhancement [33]. Meanwhile, several authors reported that tight glycemic control decreased risk of surgical site infection [34–37], although there are few studies demonstrated that tighter glycemic control prior to surgery changed the risk of AL. To clarify whether tighter preoperative glycemic control reduces the prevalence of AL, further prospective intervention studies targeted at a greater number of diabetic patients are required.

In this study, we showed the significance of HbA1c levels for predicting the development of AL after esophagogastric anastomosis for the first time. Indeed, out data indicate that the HbA1c level may be a better predictor of AL than a clinical history of diabetes. Among the 35 patients with diabetes, there was no significant difference in the incidence of AL between patients who had previously been diagnosed with diabetes and those who had not (24.1 vs 16.6 %). Moreover, while all eight patients with a HbA1c <6.5 % did not develop an AL, 8 of the 27 patients (29.6 %) with a HbA1c ≥6.5 % did develop an AL. These results indicate that the preoperative glycemic state may influence the development of AL.

Regarding the method used for anastomosis, previous meta-analyses reported that there was no significant difference between hand-sewn and stapled anastomoses in the prevalence of leak after esophagogastric anastomosis [9, 38]. However, several studies have also reported that use of a triangulating stapling technique could reduce the prevalence of AL after esophagogastric anastomosis [25, 26]. Consistent with this latter data, we also showed that AL could be significantly reduced by the use of the triangulating stapling technique for cervical esophagogastric anastomosis. Indeed, the prevalence of AL decreased significantly from 16.9 % (22/130) to 7.6 % (13/170) after the introduction of this procedure ($p = 0.018$). In our opinion, this method of anastomosis is a good alternative to the hand-sewn method for cervical esophagogastric anastomosis.

Our study had several limitations that should be addressed. First, this was a small retrospective observational study with the potential for historical bias. Therefore, further prospective studies are needed that include greater numbers of patients. Second, AL after esophagogastric anastomosis could have been attributable to the location of the anastomosis site in the neck (high or low position), the size or the conduit, or the degree of ischemia in the conduit. These factors should be considered when interpreting our data.

In conclusion, preoperative HbA1c levels were significantly associated with the development of AL after cervical esophagogastric anastomosis, suggesting that the preoperative glycemic state of a patient could influence the development of this complication. Further prospective intervention studies are required to evaluate whether improving HbA1c levels before surgery could decrease the development of AL. However, in the meantime, we recommend preoperative HbA1c screening for all patients undergoing esophagectomy.

Compliance with ethical standards

Conflicts of interest None declared.

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