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TIME SUBMITTED

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PAPER ID

115824121

Remission of type 2 diabetes one year after esophagectomy with gastric conduit reconstruction: A prospective cohort study

Xing HJ *et al.* Diabetes remission after esophagectomy

Abstract

BACKGROUND

Type 2 diabetes (T2D) remission has been widely reported after bariatric surgery, while rarely reported after esophagectomy.

AIM

To explore the incidence and predictors of T2D remission 1 year after esophagectomy with gastric conduit reconstruction.

METHODS

In this prospective study, consecutive patients from 2 tertiary hospitals who had esophageal cancer and T2D and underwent esophagectomy with gastric conduit reconstruction were studied preoperatively and at 3 months, 6 months, and 12 months postoperatively. Remission of T2D is defined as glycated hemoglobin (HbA1c) values below 6.5% without glucose-lowering medications. Related clinical information were recorded and analyzed.

RESULTS

A total of 187 patients were included. Among the patients, 24 (12.8%) discontinued antidiabetic drugs while maintained a HbA1c values below 6.5% 1 year after surgery. At baseline, patients with T2D remission were younger (63.0 ± 5.2 years *vs* 67.0 ± 6.1 years, $P = 0.002$), had higher body mass index values (body weight 68.6 ± 11.1 kg *vs* 61.2 ± 9.3 kg, $P = 0.001$; body mass index 25.5 ± 2.4 kg/m² *vs* 23.8 ± 3 kg/m², $P = 0.011$), shorter duration of T2D (4.9 ± 3.9 years *vs* 7.1 ± 3.7 years, $P = 0.008$) and higher preoperative HbA1C ($8.5\% \pm 1.7\%$ *vs* $7.7\% \pm 1.3\%$, $P = 0.042$). Multivariate logistic regression analysis showed that younger age and greater body weight were independent predictors of T2D remission after surgery.

CONCLUSION

This study reveals a significant incidence of T2D remission after esophagectomy with gastric conduit reconstruction, and remission is more frequent in patients with younger age and greater body weight.

Key Words: Esophagectomy; Gastric conduit reconstruction; Type 2 diabetes; Remission; Bariatric surgery

Xing HJ, Hu MY, Jiang YQ, Li XH, Zhu B, Wang ZQ. Remission of type 2 diabetes one year after esophagectomy with gastric conduit reconstruction: A prospective cohort study. *World J Gastrointest Surg* 2025; In press

Core Tip: In this multi-center prospective study, esophageal cancer patients with type 2 diabetes who received esophagectomy with gastric conduit reconstruction were included and followed. Results shown that diabetes remission occurred in 12.8% (24/187) of patients 1 year after surgery.

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INTRODUCTION

Esophageal cancer ranks the seventh most common type of cancer and the sixth most common cause of cancer-related death worldwide[1]. In recent years, advances in neoadjuvant strategies, perioperative care, and increased early diagnosis have achieved significant improvements in oncologic outcome for patients with esophageal cancer treated with curative intent. Surgical intervention remains the best chance for cure in regional disease and stomach is most commonly used for esophageal reconstruction. The procedure usually includes proximal gastrectomy and recently gastric tube, usually 4-6 cm, has been widely employed for the purpose of reducing anastomosis leak rate[2]. Bariatric surgery (also known as metabolic surgery) has been widely used for the treatment of morbid obesity and type 2 diabetes (T2D). Among the many available options, Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy (LSG) are currently the most widely used procedures. Multiple studies demonstrated the efficacy

of bariatric surgery in improving glucose homeostasis, reducing the need for glucose-lowering medications, inducing remission of T2D and reducing both microvascular and macrovascular complications in some patients[3]. It is reported that complete remission of T2D 1 year after bariatric surgery can be up to 74%[4].

LSG has become the most common bariatric surgery procedure, accounting for up to 60% globally[5], in large part because it is a more straightforward procedure that requires a shorter operative time than Roux-en-Y gastric bypass[6]. Typically LSG is performed laparoscopically and most of the greater curvature of the stomach is resected (gastric volume reduced by about 80%)[7]. The degree of T2D remission after LSG is generally correlated with the degree of weight loss[8,9]. Esophagectomy resembles LSG procedure to some extent, as both involve removing part of the stomach to make a sleeve-shaped tube and reduce stomach size (Figure 1). Weight loss is widely reported after esophagectomy[10]. Recently, Yang *et al*[11] reported significant weight loss and improvements in glycolipid profiles in T2D patients following esophagectomy, further supporting the potential metabolic benefits of this procedure. However, the mechanisms underlying these changes remain poorly understood. The aim of our study was to investigate whether T2D remission occurs after esophagectomy with gastric conduit reconstruction and to identify baseline predictors of its occurrence.

MATERIALS AND METHODS

The institutions of this study are two high-volume esophageal surgery centers performing over 400 cases per year combined. Detailed clinicopathological, treatment and follow-up data are maintained prospectively for all patients. The institutional research ethics committee approved this study on Jan 1, 2018 (No. CZLS2022166-A) and all patients provided written informed consent. The work was registered with the Research Registry website (<https://www.researchregistry.com/browse-the-registry#home/>) and the unique identifying number is 10673. This work has been reported in line with the STROCCS criteria[12].

Consecutive esophageal cancer patients with T2D [glycated hemoglobin (HbA1c) of $\geq 6.5\%$ or use of antidiabetic medications] scheduled to undergo potentially curative surgery between January 2019 and June 2023 were identified at the weekly tumor board and invited before surgery to participate in the study. Patients with significant dysphagia, major co-morbidity, neuropsychiatric illness, substance misuse, previous gastrointestinal surgery, cancer or using other organs instead of stomach for esophageal reconstruction were considered ineligible. All patients underwent surveillance computed tomography 3 months, 6 months and 1 year after surgery, and those developing cancer recurrence or loss of follow-up during the study interval were excluded. All patients with adequate respiratory function underwent Mckeown esophagectomy with cervical anastomosis, whereas those with significant respiratory co-morbidity had transhiatal resection with cervical anastomosis, as described previously[13,14]. To be specific, reconstruction was with a relatively narrow gastric conduit approximately 2-3 cm in width (Figure 2), with hand-sewn combined with linear stapling anastomosis. All surgeries were performed by 4 experienced attendings.

All data were collected before surgery and at 3 months, 6 months and 1 year after operation. Serial height and bodyweight measurements were obtained in the fasting state with participants wearing light indoor clothing after voiding urine. Fasting blood glucose and HbA1c were determined by automated analyzer (Cobas® 8000, Roche Diagnostics, Basel, Switzerland). The clinical and pathological stages of the malignancies were determined on the basis of the 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system for esophageal cancer[15]. The evaluation and treatment of T2D were determined by an endocrinologist each time or whenever patients reported symptoms of hypoglycemia. Changes in the prescription and dosage of glucose-lowering drugs were prespecified in detail according to the American Diabetes Association Standards (version 2017)[16]. Remission of T2D was defined as a HbA1c values below 6.5% without glucose-lowering medications[17].

Statistical analysis was performed by using the SPSS statistical package, version 26.0 (SPSS, Chicago, IL, United States). Continuous variables were presented as means \pm SD and categorical variables were expressed as frequencies. Univariable within-group comparisons were analyzed with paired Student's *t*-test or Wilcoxon signed rank test, as appropriate. Univariable between-group comparisons were performed using the Student's *t*-test or Mann-Whitney *U* test for continuous variables and χ^2 -tests or Fisher's exact test for categorical variables. Predictors of T2D remission were investigated with the use of a multiple logistic regression analysis model. All statistical analyses were two-sided and $P < 0.05$ was considered to represent statistical significance. The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

After initial screening a total of 227 patients were enrolled in this study. Two patients died from severe postoperative complication. Tumor recurrence occurred in 26 patients after surgery and 12 patients refused to follow-up. Final analyses were performed in the 187 patients who were able to complete the 1-year follow-up. The mean age was 68.4 ± 6.4 years, and 70 (37.4%) patients were older than 70 years. Most patients (157, 84%) were male. The mean body mass index (BMI) before surgery was 24.0 ± 3.0 kg/m². A majority of patients (159, 85%) had squamous cell carcinoma, and the pathological stages were 40 (21.4%) for stage I, 67 (35.8%) for stage II, 54 (28.9%) for stage III, 26 (13.9%) for stage IV, respectively. Neoadjuvant therapy was applied in 54 (28.9%) patients and adjuvant therapy was utilized in 91 (48.7%) patients. Most patients (155, 82.9%) received Mckeown esophagectomy, while 32 (17.1%) patients received transhiatal procedure. After surgery, 16 (8.6%) patients developed anastomosis leak and were managed conservatively. The mean duration of T2D was 6.8 ± 3.8 years. Before surgery, the mean fasting glucose was 7.7 ± 1.9 mmol/L and the mean HbA1c was 7.8 ± 1.4 . Oral medicine was used in 147 (78.6%) patients and 32 (17.1%) patients used insulin or combined, while 8 (4.3%) patients didn't receive any medicine for T2D before

surgery. During the 1-year follow up, 65 (34.8%) patients reported symptoms of hypoglycemia. At 1 year after surgery, 29 (15.5%) patients discontinued antidiabetic drugs, while 24 (12.8%) of them maintained a HbA1c values below 6.5%. The number of patients who had weight loss of more than 10% compared with baseline was 44 (23.5%) at 3 months, 79 (42.2%) at 6 months and 71 (38%) at 1 year, respectively. The changes of mean body weight, fasting glucose and HbA1c during the study period are shown in Table 1, and significant reductions were observed at each time point.

The study group was divided into patients with and without remission of T2D after esophagectomy. Baseline characteristics of the two groups are reported in Table 2. Patients with T2D remission were younger and had shorter duration of T2D. These patients also showed higher body weight, greater BMI and higher HbA1c before surgery compared with patients without. There were no differences between the two groups in terms of sex, BMI, histology type, pathology stage, surgery procedure, perioperative treatment, anastomosis leak, fasting glucose and insulin treatment or not before surgery. Patients with T2D remission experienced a greater reduction in body weight compared to those without remission (mean weight loss: 10.2 ± 3.1 kg *vs* 7.8 ± 2.9 kg, $P = 0.015$). To account for the potential confounding effect of weight loss on T2D remission, we performed a multivariate logistic regression analysis adjusting for baseline body weight, age, and duration of T2D. The analysis confirmed that younger age and greater baseline body weight were independent predictors of T2D remission, even after adjusting for weight loss, while shorter duration of T2D was a borderline predictor (Table 3).

DISCUSSION

It has been widely reported that altered glucose metabolism occurs after bariatric surgery, which has a treatment effect on T2D[18]. Postprandial hypoglycemia was reported in a few studies after esophagectomy, and was regarded as dumping syndrome[19-21]. In a study by Anandavadivelan *et al*[22], moderate early dumping symptom was experienced by 45% of patients after esophagectomy, while moderate late

dumping symptom was reported by 13%. However, the effect of esophagectomy on T2D control is still unclear. While our study is among the first to report T2D remission after esophagectomy, recent findings by Yang *et al*[11] also highlight significant metabolic improvements in T2D patients following this procedure, further supporting the potential benefits of esophagectomy on glucose regulation.

Our study showed that remission of T2D occurred in as many as 12.8% patients 1 year after esophagectomy, which is important in terms of preventing diabetes-related complications. Several mechanisms might be involved in its effect on diabetes control. Weight loss-dependent glucose regulatory mechanisms play an important role after bariatric surgery, and the degree of weight loss achieved with bariatric surgery is generally related to the degree of resolution of T2D[23,24]. Esophagectomy with gastric tube reconstruction is similar to vertical sleeve gastrectomy in terms of gastric volume restriction, especially when narrow gastric tube is employed. Patients in this study showed a significant decrease in body weight after esophagectomy, which is consistent with previous reports[25]. The observed remission of T2D after esophagectomy may be influenced by the significant weight loss experienced by patients postoperatively. Weight loss yields reductions in total, visceral and pancreatic adipose tissue, decreases intrahepatic levels of lipids, improved insulin sensitivity and β -cell function, all of which are expected to improve systemic glucose metabolism[26]. In our study, patients with T2D remission exhibited greater weight loss compared to those without remission, suggesting that weight loss may play a key role in the observed metabolic improvements. However, it is important to note that the relationship between weight loss and T2D remission is complex and may involve additional mechanisms, such as changes in gut hormones and neuroendocrine signaling, which warrant further investigation.

We therefore believe that the use of gastric tube plays a key role on the remission of T2D after esophagectomy. In our center, we have adopted the use of relatively narrow gastric tube, typically 2-3 cm[13], which results in smaller gastric volume comparable with LSG. By contrast, most centers use 4-6 cm gastric tube or whole stomach[27],

which means nearly 3-fold increase in gastric remnant volume, and thus weakens the effect on glucose regulation. However, this study didn't include a control group comparing the remission rate between different gastric tube diameters, and currently there is no direct evidence comparing the glucose regulatory efficiency between gastric tube and whole stomach. However, in a study by Kubota *et al*[28], longer time of hypoglycemia was found using continuous glucose monitoring (CGM) after total gastrectomy compared with distal gastrectomy, which supported the gastric remnant volume related glucose regulatory efficiency. Neuroendocrine alterations may also play a role in glucose regulation after esophagectomy. It was reported that patients demonstrated an exaggerated postprandial satiety gut hormone response after bariatric surgery, including glucagon-like peptide 1, insulin and ghrelin[29,30], suggesting weight loss-independent mechanisms for T2D resolution. Similar changes were reported after esophagectomy[25,31,32]. However, the change of related hormones was not examined in this study.

The remission rate of T2D after sleeve gastrectomy varies in different studies, from 27% in the STAMPEDE trial to 48% in the Oseberg trial 1 year after surgery[4,33], and the SM-BOSS trial reported a 5-year remission rate of 61.5%[34]. The T2D remission rate in this study is lower compared with trials on LSG. This discrepancy is partly due to patient characteristics and the severity of T2D. Participants in our study were older (68.4 ± 6.4 years), had lower BMI values (mean BMI before surgery 24.0 ± 3.0 kg/m²) and male dominant (84%). Our study showed that younger age and greater body weight were predictors for remission of T2D after esophagectomy. This is in consistent with other reports regarding bariatric surgery[35,36], and one previous study also showed that female sex was a risk factor for post bariatric hypoglycemia[37]. On the other hand, during esophagectomy gastric tube is made with the greater curvature side of the stomach to ensure enough length and blood supply for cervical anastomosis, while lesser curvature side is used during LSG. This difference may result in relatively larger stomach remnant volume after esophagectomy compared with LSG and lead to lower remission rate of T2D *via* the weight loss-dependent mechanism.

Furthermore, loss of T2D remission can occur over time after bariatric surgery. In the SLEEVEPASS randomized clinical trial, the remission rate peaked at 3 years after LSG with 46%, and dropped to 26% at 10 years[38]. In our study, 5 patients discontinued the use of antidiabetic medicine after evaluated by endocrinologist, but failed to maintain normal fasting glucose and HbA1c in subsequent follow-up. The reported recurrence rate of T2D after bariatric surgery is reciprocally progressive with an average of 2%-6% per year[39]. There is no knowledge for the forward effect of esophagectomy and gastric conduit reconstruction on glucose metabolism, which needs to be further evaluated with long-term follow-up.

As a result of this study, we believe that active glucose monitoring should be suggested for patient with T2D after esophagectomy. ² CGM provides detailed information about the 24-hours glycemic profile, including nocturnal and postprandial glycemia, which standard finger-prick blood glucose monitoring cannot provide[40]. Therefore, the use of CGM has the potential to provide a more comprehensive insight into the glycemic profile of patients following esophagectomy and guide the postoperative management of T2D. Furthermore, considering the potential treatment effect on T2D and improvement in quality of life, narrow gastric tube for esophageal reconstruction may be employed for those patients. Our study has some limitations. First, the generalizability of the results is limited by the small number of patients, narrow gastric tube used in this study ³ and a fairly short 1-year follow-up. Secondly, although our definition of remission is consistent with that used in previous landmark trials[4,41], it does not satisfy the stricter criterion suggested by Buse and colleagues[17], which requires a duration of at least 1 year of remission. Finally, while our analysis adjusted for baseline body weight and weight loss, it is possible that other factors, such as severity of T2D, swallowing difficulty before surgery, changes in eating habit after surgery, anastomosis stricture or reflux, perioperative chemotherapy or radiotherapy may have contributed to weight loss and affected glucose metabolism, therefore influencing the observed remission rates, but those factors are not investigated in detail in this study. Future studies should incorporate more detailed assessments of these

factors to better understand their contribution to T2D remission after esophagectomy. Notwithstanding, this study provides novel finding exploring the remission of T2D after esophagectomy with gastric conduit reconstruction, and might guide routine clinical practice in the foreseeable future.

CONCLUSION

In conclusion, this study reveals the significant incidence of T2D remission 1 year after esophagectomy with gastric tube reconstruction. Patients with younger age and greater body weight before surgery are more likely to develop T2D remission. The preferential use of a relatively narrow gastric tube during esophagectomy for patients with esophageal cancer and T2D has the potential to improve patient care and long-term prognosis. Adjustments in the prescription of glucose-lowering drugs should be tailored after esophagectomy.

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