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ORIGINAL ARTICLE

Effect of Sleeve Gastrectomy on Morbid Obesity with Type 1 Diabetes Mellitus; Case Series, Literature Review and Meta-Analysis

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Purpose: The aim of this study was to report our experiences of sleeve gastrectomy (SG) in obese patients with type 1 diabetes mellitus (T1DM) and to assess its metabolic outcomes through a review of the literature and a meta-analysis. **Materials and Methods:** We conducted a retrospective review of the electronic medical records of all patients who underwent bariatric surgery between January 2008 and February 2019 at a single institution. A literature search was performed using PubMed, Cochrane library, and Embase, and a meta-analysis for each direct comparison between pre- and postoperative groups was performed using the random effects DerSimonian–Laird method. **Results:** We identified three obese patients with T1DM who underwent SG. The baseline body mass index (BMI), HbA1c, and total daily insulin dose was 40.8 (37-47.4) kg/m^2, 7.1% (6%-7.7%), and 92.3 (54-113) units, respectively. After surgery, the BMI and total daily insulin dose reduced to 32.2 (30.2-37.6) kg/m^2 and 22.3 (12-40) units, respectively. However, the HbA1c increased to 7.8% (5.4%-10.8%). In the meta-analysis, the weighted mean reduction in BMI, HbA1c, and total daily insulin dose were 10.69 kg/m^2 (95% CI 7.01-14.37, P＜0.00001, I^2=0%), 0.3% (95% CI −0.10-0.71, P=0.1447, I^2=0%), and 58.52 units (95% CI 15.96-101.08, P=0.07, I^2=0%), respectively. **Conclusion:** SG showed excellent weight-reducing effects during a short follow-up period in obese patients with T1DM and improved the glycemic control by reducing insulin requirement.

Key Words: Sleeve gastrectomy, Type 1 diabetes mellitus, Bariatric surgery, Metabolic surgery, Morbid obesity

INTRODUCTION

Bariatric surgery has become a well−established treatment for patients with morbid obesity. In particular, for obese patients with type 2 diabetes mellitus (T2DM), bariatric surgery has emerged as a viable treatment option not only for weight loss but also for the treatment of metabolic diseases, particularly T2DM [1]. Recent studies have reported that in patients with T2DM, sleeve gastrectomy (SG) had an effect on glycemic control similar to that of Roux−en−Y gastric bypass (RYGB) [2,3]. The antidiabetic effects of the surgery were observed prior to significant body weight loss, and the magnitude of the effect was markedly greater than that which may be explained by weight loss alone. This weight−independent mechanism is explained by the improvement in insulin resistance due to changes in the levels of various gut−derived hormones such as Glucagon−like peptide−1 (GLP−1), Gastric inhibitory polypeptide (GIP), and Peptide YY (PYY) after bariatric surgery [4,5].

Bariatric surgery in patients with type 1 diabetes

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mellitus (T1DM) is discouraged because these patients are typically lean; moreover, the basic pathogenesis of T1DM is not insulin resistance but the autoimmune destruction of insulin-producing beta cells in the pancreas. However, the prevalence of obesity in patients with T1DM has increased, with recent studies showing that approximately 50% of patients with T1DM are either overweight or obese [6-8]. Greater degrees of obesity in patients with T1DM were associated with higher insulin requirements to achieve the glycemic goals [9]. Moreover, an increased emphasis on achieving glycemic goals and the use of intensive insulin therapy contributed to weight gain secondary to the anabolic and lipogenic actions of insulin and hyperphagia following hypoglycemic episodes [7,10]. Patients with T1DM showing clinical signs of T2DM such as obesity and insulin resistance are said to have "double diabetes" [11]. The presence of "double diabetes" can have deleterious impacts such as increases in cardiometabolic risks [12].

Bariatric surgery has recently emerged as a treatment option to escape this vicious cycle of "double diabetes." Several systematic reviews and meta-analyses have demonstrated promising results of bariatric surgery for obese patients with T1DM; however, more than 80% of the bariatric surgeries in these studies were bypass surgeries and only 12-14% were SGs [9,13,14]. There are few studies on the impact of SG on glycemic control in obese patients with T1DM and all are retrospective case series or case reports with heterogeneous results [15-20]. The aim of this study was to report our experiences of SG in obese patients with T1DM and to assess the metabolic outcomes of SG in patients with T1DM through a review of the literature and meta-analyses.

MATERIALS AND METHODS

1. Patients

We conducted a retrospective review of the electronic medical records using the bariatric service registry of all the patients who underwent bariatric surgery between January 2008 and February 2019 at a single institution. The diagnosis of T1DM was verified for all the patients by the presence of autoantibodies (islet cells, insulin, or glutamic acid decarboxylase (GAD)) or the absence of C-peptide. Comprehensive data were collected on five factors: anthropometric parameters, perioperative complications, HbA1c levels, and pre- and postoperative insulin requirements. We sufficiently explained that the main purpose of this surgery was weight loss, but not glycemic control and obtained informed consent from the patients.

2. Literature search

A literature search was performed using PubMed, Cochrane library, and Embase using combinations of the terms "bariatric surgery" or "metabolic surgery" or "sleeve gastrectomy" or "gastric bypass surgery" and "Type 1 Diabetes mellitus" or "insulin dependent diabetes mellitus" or "autoimmune diabetes" or "diabetic ketoacidosis." The last date for this search was April 1, 2019. Fig. 1 outlines our search strategy, and all the studies are listed in Table 1 [15-20].

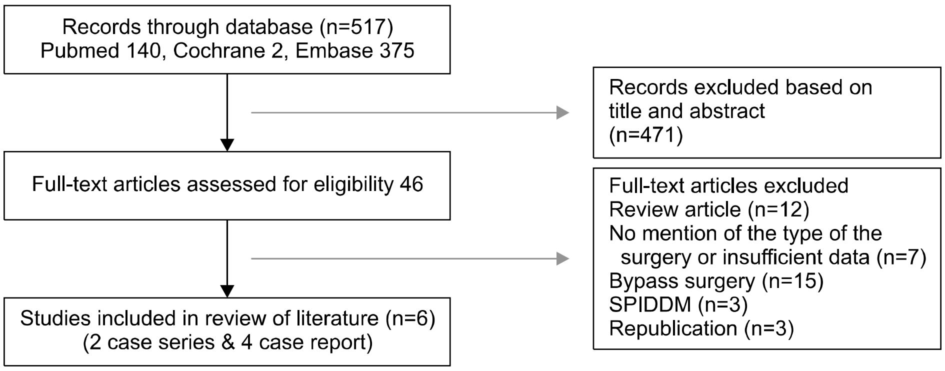

Fig. 1. Flow diagram of study selection for review of literature and meta-analyses.

Table 1. Study characteristics included in literature of review and meta-analysis

Author	Publication type	Study type	Study design	Operation (subject number)
Feilitzsch et al. [15] 2011	Conference abstract	Case report	Retrospective	SG (1)
Chuang et al. [16] 2013	Peer-reviewed journal	Case series	Retrospective	SG (1), RYGB (1)
Raab et al. [17] 2013	Peer-reviewed journal	Case series	Retrospective	SG (1), RYGB (2), BPD/DS (3)
Tang et al. [18] 2014	Peer-reviewed journal	Case series	Retrospective	SG (2), RYGB (1), GB (3)
Al Sabah et al. [19] 2017	Peer-reviewed journal	Case series	Retrospective	SG (10)
Kc et al. [20] 2018	Conference abstract	Case report	Retrospective	SG (1)

[a]SG = sleeve gastrectomy, RYGB = Roux-en Y gastric bypass, BPD/DS = biliopancreatic diversion/duodenal switch.

Table 2. Patients' demographics and baseline clinical characteristics

	All patients
Number of patients	3
Gender M/F (%)	2/1 (66.7%, 33.3%)
Age at surgery (years)	34 (28-38)
Duration of T1DM (years)	20.3 (8-28)
Follow-up period (month)	9.3 (6-14)
Initial BMI (kg/m^2)	40.8 (37-47.4)
Dyslipidemia	0
Hypertension	3

3. Statistical analysis

The mean difference and 95% confidence intervals (CIs) of each outcome were assessed by a comparison of the preoperative and postoperative groups, and the statistical heterogeneity was measured using the I^2 statistic. A meta-analysis was performed for each direct comparison between the pre- and postoperative groups using the random-effects (DerSimonian-Laird) method [21]. Depending on the values of I^2, heterogeneity was categorized as not important (0-40%), moderate (30-60%), substantial (50-90%), and considerable (75-100%). The meta-analysis was performed using Rex ver3.0.1 (RexSoft [2018] Rex: Excel-based statistical analysis software URL http://rexsoft.org/). P values < 0.05 were considered statistically significant. A subgroup analysis was performed to compare our results with those of the studies included in the review of the literature. Since all the studies had only one or two cases, except for the study by Al Sabah et al. [19] in 2017, they were integrated and named as the "other studies" group for the meta-analysis.

RESULTS

We identified three obese patients with T1DM who underwent SG. Patients' demographics is shown in Table 2. Two of them were male and one was female. The mean age at the time of surgery was 34 (28-38) years, mean duration of diabetes was 20.3 (8-28) years, and mean follow-up period was 9.3 (6-14) months. The baseline body weight was 112.7 (80-137.1) kg and body mass index (BMI) was 40.8 (37-47.4) kg/m^2. The baseline HbA1c level was 7.1% (6%-7.7%) and the total daily insulin dose was 92.3 (54-113) units. Body weight and BMI reduced to 89.1 (66.1-104) kg and 32.2 (30.2-37.6) kg/m^2, respectively, after surgery. The percentage of total weight loss was 20.2% (13.3%-29.0%) and percentage of excess BMI loss (%EBMIL) was 52.5% (39.6%-61.2%). Total daily insulin dose also decreased to 22.3 (12-40) units; however, HbA1c level increased to 7.8% (5.4%-10.8%) at the end of the follow-up period. All patients were diagnosed with primary hypertension before surgery. We thoroughly investigated the improvement of hypertension though the chart review, however, there were insufficient data to determine the improvement.

1. Case 1

The patient was a 38-year-old man who was diagnosed with T1DM at 25 years ago and was undergoing hemodialysis after he was diagnosed with chronic kidney disease (CKD) 11 years ago. He also had hypertension and chronic hepatitis B. At baseline, his BMI was 37.9 kg/m^2 (178 cm, 120 kg); HbA1c level, 7.6%; and total daily insulin dose, 110 units. He underwent SG in March 2016 without perioperative complications. Eight months after

SG, his BMI decreased to 32.8 kg/m^2 (body weight, 104 kg) and the total daily insulin dose decreased to 40 units. However, his HbA1c level increased to 10.8%.

2. Case 2

The patient was a 36-year-old man who was diagnosed with T1DM and CKD requiring hemodialysis 28 years ago. He also had hypertension, gout, hypothyroidism, complex regional pain syndrome and depression. At baseline, his BMI was 47.4 kg/m^2 (170 cm, 137.1 kg); HbA1c level, 6.0%; and total daily insulin dose, 113 units. He underwent SG in February 2018 without perioperative complications. Fourteen months after SG, his BMI decreased to 33.7 kg/m^2 (body weight, 97.4 kg), HbA1c decreased to 5.4%, and the total daily insulin dose decreased to 15 units.

3. Case 3

The patient was a 28-year-old woman who was diagnosed with T1DM 8 years ago. She had been taking levothyroxine after being diagnosed with hypothyroidism in 2014. She was newly diagnosed with hypertension during the preoperative evaluation and was prescribed medication. At baseline, her BMI was 37.0 kg/m^2 (148 cm, 81 kg); HbA1c level, 7.7%; and total daily insulin dose, 54 units. She underwent SG in February 2019. On postoperative day 1, she showed clinical signs (nausea and intermittent vomiting), and her diabetes was not sufficiently controlled to check blood sugar test (BST) of more than 300 mg/dl. On postoperative day 2, her blood pH was 7.12, HCO_3 was 11.6 nmol/L, anion gap was 22 on arterial blood gas analysis, ketone level was 3+ on urinalysis, and BST was 350 mg/dL. She was diagnosed with diabetic ketoacidosis, treated in an intensive care unit for 2 days, and then discharged after 3 days without any other complications. Six months after SG, her BMI decreased to 30.2 kg/m^2 (body weight, 66.1 kg), HbA1c level decreased to 7.2%, and total daily insulin dose decreased to 12 units.

Metabolic profile of each patients before and after surgery is summarized in Table 3.

Table 3. Metabolic profile of each patients before and after sleeve gastrectomy

Case number	Gender	Age (years)	Duration of T1DM (years)	Follow-up period (month)	BMI before/after surgery (kg/m^2)	BMI loss (kg/m^2)	%EBMIL (%)	HbA1c before/after surgery (%)	Change in HbA1c	Insulin dosage before/after surgery (units)	Change in dosage	Other improved comorbidities	Complications
Case 1	M	38	25	8	37.9/32.8	5.1	39.5	7.6/10.8	+3.2	110/40	−70	NA	None
Case 2	M	36	28	14	47.4/33.7	13.7	61.2	6/5.4	−0.6	113/15	−98	NA	None
Case 3	F	28	8	6	37/30.2	6.8	56.7	7.7/7.2	−0.5	54/12	−42	NA	DKA
All (mean value)		34	20.3	9.3	40.8/32.2	8.6	52.5	7.1/7.8	+0.7	92.3/22.3	−70	NA	33.3% DKA

DKA = diabetic ketoacidosis; NA = not applicable.

4. Outcomes from the review of literature and meta-analysis

Six studies were included, producing a pooled dataset of 16 patients in the literature review. All the studies were non-randomized retrospective case series or case reports. The mean pre-operative BMI was 43.0 kg/m^2; HbA1c level, 8.7%; and total daily insulin dose, 112.5 units. The mean age at operation was 34 years, 69% of the patients were women (11 patients), and the mean follow-up period was 32.3 months.

1) BMI

Pooled analysis of 16 patients from the 6 studies demonstrated that the weighted mean reduction in BMI was 10.69 kg/m^2 (95% CI 7.01–14.37, P<0.00001, I^2=0%), whereas the BMI reduction in our study was 8.2 kg/m^2 (95% CI 0.38. 16.02, P=0.0398, I^2=not applicable) (Fig. 2) [19].

2) HbA1c

Pooled analysis of 15 patients from the 6 studies demonstrated that the weighted mean reduction in HbA1c was 0.3% (95% CI −0.10–0.71, P=0.1447, I^2=0%), whereas the HbA1c increase in our study was 0.7% (95% CI −4.94–3.54, P=0.7465, I^2=not applicable) (Fig. 3) [19].

3) Total daily insulin dose

Pooled analysis of 16 patients from the 6 studies demonstrated that the weighted mean reduction in insulin requirement was 58.52 units (95% CI 15.96–101.08, P=0.07, I^2=0%), whereas the insulin requirement reduction

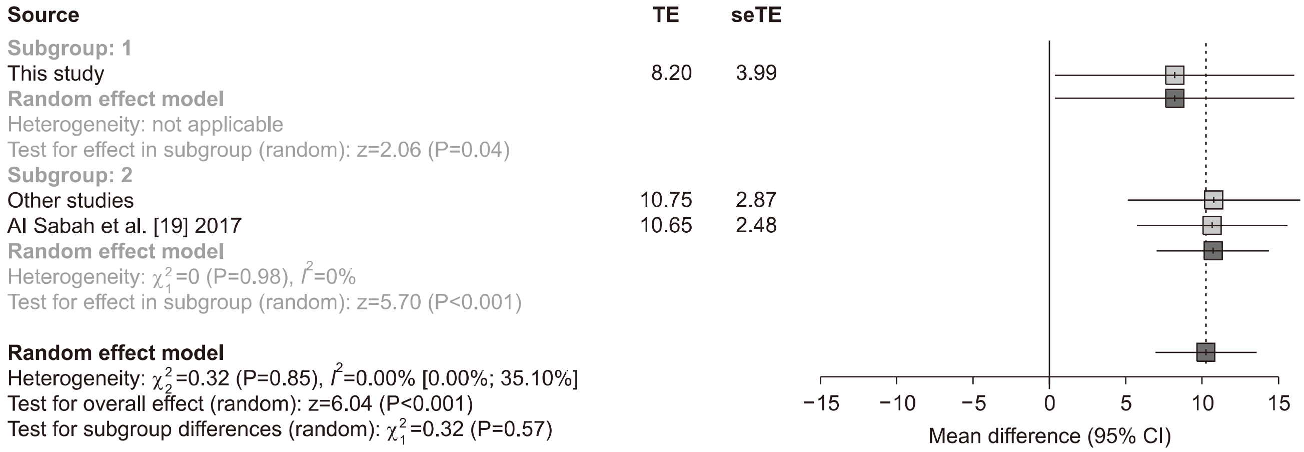

Fig. 2. Forest plots demonstrating changes in BMI following sleeve gastrectomy in obsess patients with type 1 diabetes mellitus.

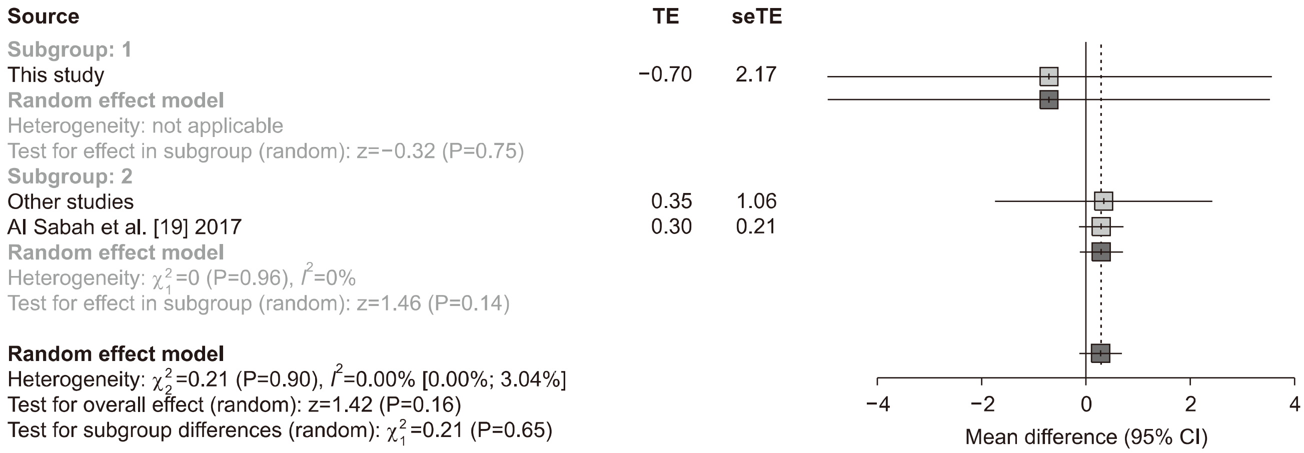

Fig. 3. Forest plots demonstrating changes in HbA1c following sleeve gastrectomy in obsess patients with type 1 diabetes mellitus.

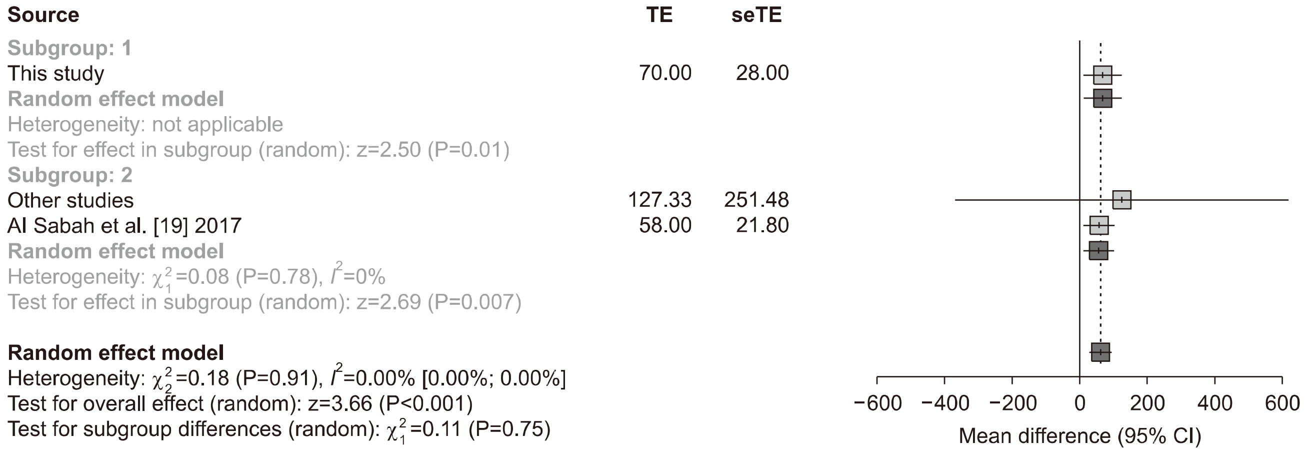

Fig. 4. Forest plots demonstrating changes in total daily insulin dose following sleeve gastrectomy in obsess patients with type 1 diabetes mellitus.

in our study was 70 units (95% CI 15.12–124.88, P=0.012, I^2=not applicable) (Fig. 4) [19].

Table 4 [15–20] summarizes the key results from this study and the studies included in the literature review.

DISCUSSION

This study demonstrated that SG is beneficial in reducing the weight and total daily insulin dose of obese patients with T1DM. However, no significant reduction was observed in HbA1c levels. To the best of our knowledge, this is the first study to report the effect of SG in obese patients with T1DM in East Asia.

Our study showed that the %EBMIL was 52.5% at a mean follow-up period of 9.3 months and the meta-analysis demonstrated that the %EBMIL was 59.3% at a mean follow-up period of 32.3 months. This figure is comparable with the BMI reduction after SG in patients with T2DM in randomized controlled trials [2,3]. In addition, the BMI reduction of 10.69 kg/m^2 shown in our meta-analysis was not significantly different from that in the meta-analysis of T1DM (11.87 kg/m^2) which included the majority of patients (83%) who underwent bypass surgeries such as RYGB and biliopancreatic diversion [9]. This is because the main mechanism of weight loss in all kinds of bariatric surgery is through restriction of calorie intake due to the reduction in gastric volume.

This study showed that the decreases in the total daily insulin dose after SG, however, did not lead to any significant reduction in HbA1c levels. The reduction in the insulin requirement can be explained by the improvement in insulin resistance due to weight loss and the decrease in caloric intake. Caloric restriction leads to a reduced requirement of fast-acting insulin before meals and improves hepatic insulin sensitivity, resulting in a reduced basal insulin demand [22]. In addition, the diminishing lipotoxicity in the liver and skeletal muscles and improvements in the obesity-associated pro-inflammatory environment following weight loss can also lead to improved insulin resistance [19,23]. The lack of improvement in HbA1c levels observed in this study despite the beneficial weight loss should be seen in light of the reduction in insulin dose. A comparison of the results of the meta-analysis between our patients and those of the other studies revealed that our patients showed a greater extent of insulin dose reduction even though they had lower weight loss than those in the other studies; however, their HbA1c levels increased. This suggests that the greater the insulin dose adjustment range, the lower the effect on the HbA1c level. No improvements in HbA1c may also be related to the lack of functioning beta cells, that is, the patient did not benefit from the increased GLP-1-induced insulin secretion that was prominent after RYGB in patients with T2DM [24]. Although the mean of HbA1c increased after surgery, that of two patients decreased

Table 4. Summary of key results from the studies included in literature review and meta-analysis

Author	No. of patients	Gender	Age (years)	Duration of T1DM (years)	Follow-up period (month)	BMI before/after surgery (kg/m^2)	BMI loss (kg/m^2)	%EBMIL (%)	HbA1c before/after surgery (%)	Change in HbA1c	Insulin dosage before/after surgery (units)	Change in dosage	Other improved comorbidities	Complications
Feilitzsch et al. [15] 2011	1	F	37	12	6	46/37	11	42.9	10/NA	NA	700/60	−690	NA	NA
Chuang et al. [16] 2013	1	M	19	10	12	42.3/30.2	12.1	69.9	8.6/8.8	+0.2	115/90	−25	Dyslipidemia OSA QoL	DKA, mild hypoglycemic episodes
Raab et al. [17] 2013	1	F	38	19	12	37.3/25.3	12.0	97.6	7.4/7.2	−0.2	88.6/48	−39.4	NA	NA
Tang et al. [18] 2014	1	F	38	28	31	54.5/40.5	14.0	47.5	9.9/ 10.1−11.4	+0.2−1.5	46/25	−21	NA	NA
	1	F	31	13	9	49.1/37.6	11.5	47.7	6.7/ 7.8−8.3	+1.1−1.6	60/26	−34	NA	NA
Al Sabah et al. [19] 2017	10	F/5 (50%)	34.1±12.6	NA	48 (6−96)	41.9±5.4/ 31.4±8.4	10.5*	74.4±25.3[a]	8.6±1.2/ 8.3±1.4	−0.3	76±68/ 18±18	−58*	No improvement of cholesterol level	18.2% hypoglycemia
Kc et al. [20] 2018	1	F	46	36	3	39/33.1	5.9	42.1	9.8/8	−1.8	31/27.6	−3.4	NA	None

*$P < 0.05$.
[a]% Excess weight loss, NA = not applicable, OSA = obstructive sleep apnea, QoL = quality of life, DKA = diabetic ketoacidosis.

after surgery except one patient. That might be caused by small population in this study. One of the three meta-analyses [13] reported so far on the effect of bariatric surgery on obese patients with T1DM was consistent with the results of our study; however, two meta-analyses showed significant improvement in not only the total daily insulin requirement but also the HbA1c levels [9,14].

So far, it is unclear as to which surgical procedure is the best option for obese patients with T1DM. Most importantly, during bariatric surgery in patients with T1DM, glucose control after surgery must be monitored. Postoperative ketoacidosis and recurrent hypoglycemia have been reported in several studies, and Al Sabah et al. [19] demonstrated that 18.2% of patients experienced severe hypoglycemia after SG [16]. Changes in gut anatomy after RYGB result in glucose variability, and there are alterations in glucose absorption kinetics. Some studies reported higher and earlier postprandial glucose peaks followed by rapid decreases in glucose levels, supposedly due to the rapid delivery of carbohydrates to the jejunum. This may make it difficult to match the insulin administration to the glycemic state, which leads to either hyperglycemia or hypoglycemia [25]. Because of the risk of food intolerance and gastrointestinal symptoms, patients may prefer injecting insulin after meals, which is associated with increased glucose variability and suboptimal postprandial glucose profiles in patients with T1DM [16]. Carbohydrate absorption is more predictable in SG, and it may be more appropriate in obese patients with T1DM [9,26]. In addition, preserving the pylorus prevents the possibility of dumping syndrome and extreme variations in postprandial glycemia, which can be challenging to manage in patients with T1DM [27].

This study has several limitations associated with its retrospective nature, lack of randomization, small sample size, and short-term follow-up period. To date, research in this field has been initiated in the form of case studies and case series; therefore, all studies currently occupy low evidence levels.

CONCLUSION

SG showed excellent weight-reducing effects within a short follow-up period in obese patients with T1DM and improved glucose control by reducing insulin requirement. However, while interpreting the results, we must consider that the level of evidence is low as most of the studies reporting bariatric surgical outcomes in patients with T1DM are still in the early phase with small study populations. Therefore, further research including long-term comprehensive studies or randomized controlled trials in conjunction with mechanistic studies is necessary to better clarify the role of SG.

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