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Bariatric surgery versus medical treatment in mildly obese patients with type 2 diabetes mellitus in Japan: Propensity score-matched analysis on real-world data

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ABSTRACT
Aims/Introduction: To compare glycemic control 1 year after treatment in patients with mildly obese (body mass index 27.5–34.9 kg/m^2) type 2 diabetes mellitus who underwent bariatric surgery (BS) to those who received medical treatment (MT) in Japan.
Materials and Methods: A retrospective study using real-world data was carried out in electronic medical records from a tertiary care hospital and in the Japanese Medical Data Center Inc. claim database from 2008 to 2019. Each patient was propensity score-matched between the BS and the MT group by age, sex, body mass index, glycated hemoglobin and type 2 diabetes mellitus duration, and compared from the index date to the 1 year post-index.
Results: The study included 78 patients in the BS group and 238 patients in the MT group. The mean body mass index in the BS and the MT group was 32.1 and 32.0 kg/m^2, respectively. In the BS group, the patients underwent either laparoscopic sleeve gastrectomy with or without duodenojejunal bypass. The diabetes remission rate (glycated hemoglobin <6.5% without diabetes medication) at 1 year was 59.0% in the BS group and 0.4% in the MT group (P < 0.0001). Optimal glycemic control of glycated hemoglobin <7.0% was achieved in 75.6% in the BS group and in 29.0% in the MT group (P < 0.0001). The median monthly drug costs for metabolic syndrome decreased from $US126.5 (at baseline) to $US0.0 (at 1 year) in the BS group, whereas it increased from $US52.4 to $US58.3 in the MT group.
Conclusions: BS for mildly obese patients with type 2 diabetes mellitus is more clinically- and cost-effective than MT in Japan.

INTRODUCTION
The number of patients with diabetes mellitus is increasing at an alarming rate, making diabetes one of the leading causes of mortality and cardiovascular events worldwide[1]. The International Diabetes Federation estimates that the global number of patients with diabetes is 463 million in 2019 and will increase to 700 million by 2045[2]. In Japan, the number of patients with diabetes was 3.29 million in 2017 and an increase was seen from 3.17 million patients in 2014[3].

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As the number of patients with diabetes increases, the associated medical costs rise in tandem. The International Diabetes Federation estimates that global health expenditures as a result of diabetes were $US760 billion in 2019, and will be $US845 billion by 2045[2]. According to the 2018 National Medical Expense Survey in Japan, annual total medical costs were approximately $US434 billion[4]. The costs for diabetes were $US12 billion, accounting for 3% of the total annual medical costs (all costs were $US1.00 = ¥100)[4].

Non-surgical treatment for type 2 diabetes mellitus is comprised of lifestyle modification along with pharmacological management of glucose intolerance and comorbidities, especially dyslipidemia and hypertension. Although medical management of diabetes is clearly worthwhile, it is often difficult to achieve treatment goals. Shortcomings include incomplete response to medication, difficulty in achieving lifestyle and medical regimen compliance, side-effects, and cost. Indeed, according to the Japan Diabetes Clinical Data Management Study Group (JDDM) in 2019, 49.8% of type 2 diabetes mellitus patients had glycated hemoglobin (HbA1c) <7.0%, and 13.3% had uncontrolled HbA1c ≥8.0%[5]. As many diabetes patients in a community setting do not meet the treatment goals, other avenues should be explored for the management of type 2 diabetes mellitus.

Bariatric surgery (BS) is effective in type 2 diabetes mellitus through multiple mechanisms, not only as a result of weight loss[6]. Recent randomized controlled trials comparing surgical and non-surgical treatments for diabetes have uniformly shown surgical treatments to be superior in improving glycemic control and other metabolic end-points[7]. Considering the body of evidence, the 2nd Diabetes Surgery Summit guidelines published in 2016 suggested expanding the indications for BS to include patients with inadequately controlled type 2 diabetes mellitus and body mass index (BMI) as low as 30 kg/m^2, and down to 27.5 kg/m^2 for Asian patients. This is specifically important in Asia, as Asian people are prone to central obesity and show susceptibility to metabolic disorders at a lower BMI than Westerners[8,9]. In Japan, there are some case series showing favorable outcomes of BS in mildly obese patients with type 2 diabetes mellitus[10,11]. However, there are no previous studies comparing BS with medical treatments (MT) in patients from Japan. The present study compared the bariatric patient data from a tertiary care hospital (Yotsuya Medical Cube) with Japanese Medical Data Center Inc. (JMDC) data, including patients who received MT for type 2 diabetes mellitus.

The present study aimed to evaluate 1-year type 2 diabetes mellitus treatment effects, including clinical and economic outcomes for BS (laparoscopic sleeve gastrectomy [LSG] and laparoscopic sleeve gastrectomy with duodenojejunal bypass [LSG-DJB]) versus MT for mildly obese patients in Japan (including pre-obesity and obesity class I according to the World Health Organization Obesity Criteria[12], with 27.5 kg/m^2 ≤ BMI < 35 kg/m^2).

MATERIALS AND METHODS

Study design and patient sampling

The present study consisted of retrospective analysis of data within an administrative database and hospital electronic medical records. The flowchart in Figure 1 shows the attrition process and the number of eligible patients in the present study. For the MT group, index dates were those within 6 months after the first administration of a drug for type 2 diabetes during which HbA1c was ≥6.5% (index dates presented between January 2008 and June 2019). For the BS group, the index date was defined as the date of BS. All included patients had to meet all the following criteria: HbA1c ≥6.5% (at or before the index date); 27.5 kg/m^2 ≤ BMI < 35 kg/m^2 (on date closest to the index date); and age 18–65 years at the index date. Additional inclusion criteria were applied for each treatment group.

The BS group included all patients meeting the aforementioned criteria who had undergone BS (LSG, LSG-DJB) and those under a physician's care for type 2 diabetes mellitus treatment for at least 6 months at Yotsuya Medical Cube. The MT group included all eligible patients (as per the aforementioned criteria) who had been prescribed a type 2 diabetes mellitus drug (World Health Organization anatomical therapeutic chemical classification system code starts with 'A10') for >6 months' duration from the most recent type 2 diabetes mellitus diagnosis (ICD-10 code E11 or E14) within the JMDC database. These patients were also required to have HbA1c and BMI data for 1 year (±3 months) from the index date.

Patients were excluded for any of the following reasons: type 1 diabetes within 36 months of the index date; any cardiovascular event within 6 months pre-index; any diagnosis of congestive heart failure or angina pectoris within the 6 months pre-index; any diagnosis of pulmonary embolus or thrombophlebitis within 6 months pre-index; cancer of any kind within 36 months pre-index; serum creatinine >2.0 mg/dL; any history of stomach surgery, pancreatic surgery or splenectomy within 36 months pre-index; diagnosis of gastric or duodenal ulcer within 6 months pre-index; any history of intra-abdominal sepsis within 36 months pre-index; diagnosis of HIV, tuberculosis, malaria, chronic hepatitis B or C, cirrhosis, or inflammatory bowel disease within 36 months pre-index; or diagnosis of alcohol or drug dependency within 6 months pre-index.

The study conformed to the provisions of the Declaration of Helsinki and its late amendments. The institutional ethics committee of Yotsuya Medical Cube approved the research protocol (YCR20014) on 16 November 2020.

Data source

BS group

The BS group comprised patient-level data extracted from the Yotsuya Medical Cube electronic medical records, including 119 patients who had BS (LSG, LSG-DJB) from January 2008 to June 2019, as shown in Figure 1. Since 2007, the hospital has carried out LSG-DJB as an alternative to laparoscopic Roux-en-Y gastric bypass[9]. The choice between LSG and LSG-DJB was determined based on patient condition.

MT group

Patients who met eligibility criteria for the MT cohort were identified within the JMDC database. JMDC is an epidemiological receipt database that has accumulated receipts (inpatient, outpatient and dispensing) and medical examination data from multiple health insurance associations in Japan. The cumulative dataset includes approximately 7.4 million subjects as of September 2019, and covers approximately 25% of the

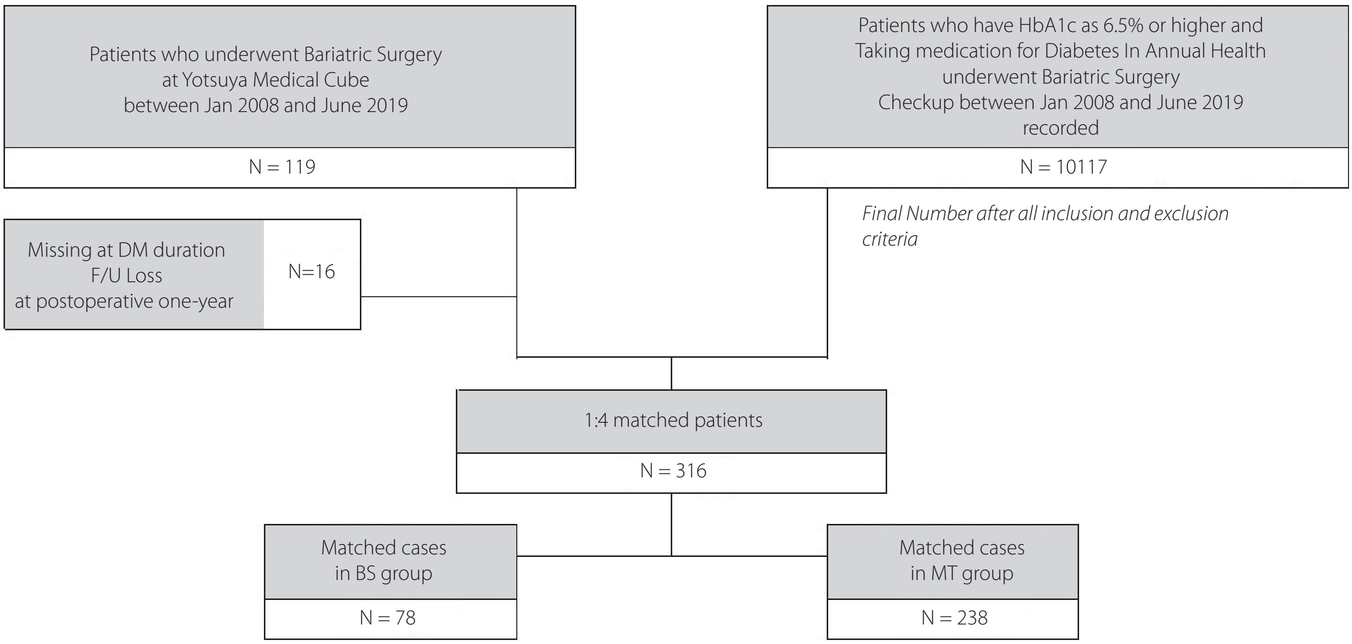

Figure 1 | Flowchart showing the process of selecting individuals for inclusion in the study. The total number of patients in the target period was 119 in the bariatric surgery group and 10,117 in the medical treatment group. Through propensity score matching, 78 patients in the bariatric surgery group and 238 patients in the medical treatment group were extracted. BS, bariatric surgery; F/U, follow up; HbA1c, glycated hemoglobin; MT, medical treatment.

population in health insurance associations. The MT group extracted from JMDC comprised 10,117 patients, including those who had HbA1c of ≥6.5% and were taking medication for diabetes in annual health checkups from January 2008 to June 2019 (Figure 1).

Drug classification used for medical costs

The cost basis for MT was obtained by evaluating the utilization of drugs within three categories: (i) antidiabetic; (ii) antihypertensive; and (iii) lipid-lowering drugs, all of which were identified using JMDC drug codes and World Health Organization anatomical therapeutic chemical classification system codes.

Only prescriptions received within 30 days pre-index or 30 days before 1 year post-index were extracted. The unit price of each drug was based on the Japanese official drug price list as of April 2020.

Objectives

The primary objective was to compare 1-year diabetes remission rates between BS and MT for type 2 diabetes mellitus patients. Diabetes remission at the 1-year mark was determined by HbA1c <6.5% without diabetes medication. The secondary objective was to assess between-group differences from the index date to the 1-year follow-up time point in HbA1c and BMI values. The following evaluations were also explored: lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides), blood pressure (systolic blood pressure, diastolic blood pressure) and cardiovascular disease risk based on the Framingham risk score. Medical costs of the BS group and the MT group were also compared. Drug treatment costs for type 2 diabetes mellitus, hypertension and dyslipidemia were calculated by the prescriptions of these drugs. Comparing the monthly drug treatment costs were based on the 1-month pre-index date and the 1-month at the 1-year post-index date.

Statistical analysis

Frequency counts and proportions were provided for categorical variables. Means, medians and standard deviations were provided for continuous variables. The BS cohort was matched by age, sex, BMI, HbA1c, type 2 diabetes mellitus duration, and index year to the MT group using propensity score matching. Patients were matched (BS : MT) at a 1:4 ratio using the nearest neighbor technique, without replacement, enforcing a caliper of 0.15, where n was determined by the relative sizes of the matched comparison groups. For the objective judgement, we used the absolute standardized mean difference, to check the balance. With a threshold being recommended for declaring imbalance[13]. The present study used the incomplete matching so that the maximum sample size could be analyzed for this study.

In matched samples, the Student's t-test or Mann–Whitney U-test were used, as appropriate, to compare between-group differences in changes in HbA1c, BMI, lipid profile and blood pressure between baseline and 1-year follow up. The χ^2-test or Fisher's exact test were used to compare categorical variables between the BS and MT groups.

Logistic regression was used to quantify the effect of BS versus MT on rates of diabetes remission at the 1-year follow-up time point after controlling for age, BMI, HbA1c at index date, duration of type 2 diabetes and insulin use at index date. The covariate-adjusted remission rate for each group was computed from the final logistic regression model. Treatment costs for type 2 diabetes mellitus or all metabolic diseases (type 2 diabetes mellitus, hypertension and dyslipidemia) were modeled by a generalized linear model with log link and gamma distribution while controlling the same covariates. The beta coefficients were exponentiated for ease of interpretation. All analyses were carried out using R (version 4.0.3; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of BS and MT groups

Table 1 shows the characteristics of the study sample before and after propensity score matching. There were 78 patients in the BS group, with a mean age of 47.9 ± 9.6 years. The preoperative mean BMI and HbA1c were 32.1 ± 1.8 kg/m^2 and 7.9 ± 1.1%, respectively. The mean duration of type 2 diabetes mellitus from diagnosis was <8 years in 46 patients (59.0%), and was ≥8 years in 32 patients (41.0%). In the MT group, there were 238 patients, with a mean age of 47.8 ± 7.7 years. At index, mean BMI and HbA1c were 32.0 ± 2.0 kg/m^2 and 7.9 ± 1.4%, respectively. The mean duration of type 2 diabetes mellitus from diagnosis was <8 years in 176 patients (74.0%), and was ≥8 years in 62 patients (26.0%). Both the BS and MT groups were well balanced in terms of sex, and there was no significant difference in mean age.

Diabetes remission in BS and MT groups

Table 2 shows diabetes remission rates and HbA1c outcomes in both groups at the 1-year post-index date. The diabetes remission rate was 59.0% (46 patients) in the BS group, and 0.4% (one patient) in the MT group, representing a statistically significant difference between the two groups (P < 0.0001). In the BS group, the mean HbA1c at index was 7.9 ± 1.1%, and decreased to 6.3 ± 1.0% at 1-year post-index. In contrast, in the MT group, the mean HbA1c at index was 7.9 ± 1.4% and 7.9 ± 1.5% at 1-year post-index. In the BS group, 59 patients (75.6%) achieved HbA1c <7.0% compared with 69 patients (29.0%) in the MT group (P < 0.0001). Notably, the number and proportion of patients with HbA1c ≥8% on the index date were higher in the BS group, comprising 32 patients (41.0%) in the BS group versus 84 patients (35.3%) in the MT group (Table 1). Despite this, there were four patients (5.1%) in the BS group and 87 patients (36.6%) in the MT group with HbA1c ≥8% at 1-year follow up (Table 2). At the 1-year post-index date, the BS group included 59 patients (75.6%) without drug treatment, versus the MT group, which included 214 patients (89.9%) who were receiving oral medication.

Comparison of secondary measures

Mean changes in HbA1c and BMI within the BS group were −1.6 ± 1.2% and −7.5 ± 2.8 kg/m^2, whereas those in the MT group were 0.0 ± 1.2% and −0.4 ± 1.3 kg/m^2 (P < 0.0001; Table 3). Other metabolic parameters, such as blood pressure, low-density lipoprotein cholesterol and triglycerides, also significantly decreased in the BS group when compared with the MT group, whereas high-density lipoprotein cholesterol significantly increased in the BS group versus the MT group. At the 1-year change in comparing Framingham risk scores, 77 patients in the BS group had a mean change of −1.6 ± 3.0 point, whereas 64 patients in the MT group had a mean change of −0.1 ± 2.7 points (P < 0.003).

Comparison of drug cost

Table 2 shows a patient number comparison of prescription status on antidiabetic drugs for both groups at the 1-year post-index date. In the BS group, the number of patients with no antidiabetic drugs was 59 patients (75.6%). In contrast, in the MT group, the number of patients with no antidiabetic drugs was 18 patients (7.6%), in the 1-month before the 1-year post-index date. The continuation rate of antidiabetic drugs (oral medication + injectable agent, oral medication only) differed widely between the BS group (20.5%, 16 patients) and MT group (92.4%, 220 patients).

Comparisons of monthly drug treatment costs between both groups are shown in Table 4 and Figure 2 for the index date and 1-year post-index date. In the BS group, monthly drug treatment costs (median) on the index date were $US70.6 for antidiabetic drugs, $US2.0 for antihypertensive drugs, $US14.3 for lipid-lowering drugs and the cost for all of these drugs was $US0.0 at the 1-year post-index date. In the MT group, monthly drug treatment costs (median) on the index date were $US40.9 for antidiabetic drugs, $US2.8 for antihypertensive drugs, $US1.9 lipid-lowering drugs, and at the 1-year post-index date were $US46.4 for antidiabetic drugs, $US2.9 for antihypertensive drugs and $US0.0 for lipid-lowering drugs. The monthly drug treatment costs for all metabolic-related therapies in 78 patients in the BS group decreased from a median of $US126.5 on the index date to $US0.0 at the 1-year post-index date. The monthly drug treatment costs for all metabolic diseases in 238 patients in the MT group increased from a median of $US52.4 on the index date to $US58.3 at the 1-year post-index date.

Logistic regression analysis of diabetes remission and drug costs

Table 5 shows output from the logistic regression analysis for diabetes remission. Diabetes remission was significantly higher in the LSG group with an odds ratio of 3153.2 (95% confidence interval [CI] 257.3–38,648.0), and in the LSG-DJB group with

Table 1 | Baseline characteristics of obese patients with type 2 diabetes before and after propensity score matching by treatment group

Variable	Before PSM		AMD	After PSM		AMD
	BS (*n* = 103)	MT (*n* = 10,117)		BS (*n* = 78)	MT (*n* = 238)	
Age at index date, mean ± SD (years)	47.7 ± 9.9	50.7 ± 7.0	0.344	47.9 ± 9.6	47.8 ± 7.7	0.06
Sex, male, *n* (%)	49 (47.6%)	8,648 (85.5%)	0.379	39 (50.0%)	121 (50.8%)	0.009
BMI level at index date, mean ± SD (kg/m^2)	32.2 ± 1.9	30.3 ± 2.0	0.986	32.1 ± 1.8	32.0 ± 2.0	0.006
HbA1c level at index date, mean ± SD (%)	8.0 ± 1.1	7.6 ± 1.1	0.354	7.9 ± 1.1	7.9 ± 1.4	0.044
Duration of type 2 diabetes, *n* (%)						
<1 year	13 (12.6%)	2,779 (27.5%)	0.148	11 (14.1%)	53 (22.3%)	0.032
≤1 and <4 years	17 (16.5%)	6,240 (61.7%)	0.452	17 (21.8%)	71 (29.8%)	0.018
≤4 and <8 years	18 (17.5%)	947 (9.4%)	0.081	18 (23.1%)	52 (21.9%)	0.013
≥8 years	55 (53.4%)	151 (1.5%)	0.519	32 (41.0%)	62 (26.1%)	0.037
			***P*-value (χ^2-test)**			***P*-value (χ^2-test)**
HbA1c level group at index date, *n* (%)						
6.5–6.9 (mild)	15 (14.6%)	3,304 (32.7%)	0.0001	12 (15.4%)	68 (28.6%)	0.0665
7.0–7.9 (moderate)	45 (43.7%)	4,065 (40.2%)		34 (43.6%)	86 (36.1%)	
≥8.0 (severe)	43 (41.8%)	2,748 (27.2%)		32 (41.0%)	84 (35.3%)	
Patients being treated for type 2 diabetes at 1-month pre-index date, *n* (%)	96 (93.2%)	10,117 (100.0%)	<0.0001	73 (93.6%)	238 (100.0%)	0.0008
Patients being treated for hypertension at 1-month pre-index date, *n* (%)	50 (48.5%)	5,837 (57.7%)	0.0768	39 (50.0%)	136 (57.1%)	0.3320
Patients being treated for dyslipidemia at 1-month pre-index date, *n* (%)	57 (55.3%)	5,276 (52.2%)	0.5853	45 (57.7%)	124 (52.1%)	0.4663

AMD, absolute mean difference; BMI, body mass index; BS, bariatric surgery; HbA1c, glycated hemoglobin; MT, medical treatment; PSM, propensity score matching; SD, standard difference.

Table 2 | Primary outcomes in the matched obese patients with type 2 diabetes by treatment group

Variable	Total (*n* = 316)	BS (*n* = 78)	MT (*n* = 238)	*P*-value
Diabetes remission at 1-year post-index date†, *n* (%)				
Yes	47 (14.9%)	46 (59.0%)	1 (0.4%)	<0.0001
No	269 (85.1%)	32 (41.0%)	237 (99.6%)	
HbA1c level at 1-year post-index date‡, Mean ± SD (%)	7.5 ± 1.5	6.3 ± 1.0	7.9 ± 1.5	<0.0001
HbA1c level group at 1-year post-index date§, *n* (%)				
<6.5	72 (22.8%)	49 (62.8%)	23 (9.7%)	<0.0001
6.5–6.9 (mild)	56 (17.7%)	10 (12.8%)	46 (19.3%)	
7.0–7.9 (moderate)	97 (30.7%)	15 (19.2%)	82 (34.5%)	
≥8.0 (severe)	91 (28.8%)	4 (5.1%)	87 (36.6%)	
<7.0	128 (40.5%)	59 (75.6%)	69 (29.0%)	<0.0001
≥7.0	188 (59.5%)	19 (24.4%)	169 (71.0%)	
Treatment of type 2 diabetes at 1-year post-index date§, *n* (%)				
Oral medication + injectable agent	6 (1.9%)	0 (0.0%)	6 (2.5%)	<0.0001
Oral medication only	230 (72.8%)	16 (20.5%)	214 (89.9%)	
Injectable agent only (Insulin)	2 (0.6%)	2 (2.6%)	0 (0.0%)	
Injectable agent only (others)	1 (0.3%)	1 (1.3%)	0 (0.0%)	
None	77 (24.47%)	59 (75.6%)	18 (7.6%)	

%: *n* / (number of total participants in each category) × 100. BMI, body mass index; BS, bariatric surgery; HbA1c,; MT, medical treatment; SD, standard difference. †Glycated hemoglobin (HbA1c) level <6.5% and no treatment of type 2 diabetes at 1-year post-index date. ‡The outcome did statistical processing by independent *t*-test (if normality test was not significant, Mann–Whitney test was carried out instead of independent *t*-test). §If cells with an expected frequency of ≤5 exceed 20%, Fisher's exact test was carried out instead of the χ^2-test.

an odds ratio of 2121.9 (95% CI 174.6–25,782.2) compared with the MT reference group (*P* < 0.001 respectively).

As shown in Table 6, type 2 diabetes mellitus drug costs 1 year after the index date were significantly lower in both surgical groups (LSG and LSG-DJB) compared with the reference group (MT). Type 2 diabetes mellitus drug costs using the beta coefficient were 0.018 in the LSG group (95% CI 0.011–0.029) and 0.016 in the LSG-DJB group (95% CI 0.01–0.026), both lower than those in the MT group (*P* < 0.001).

As shown in Table 7, the drug costs for all metabolic disorders-related drugs at the 1-year post-index date were also significantly lower in both surgical groups (LSG and LSG-DJB) compared with the reference group (MT). The drug costs using the beta coefficient for all metabolic diseases were 0.104 in the LSG group (95% CI 0.063–0.17) and 0.122 in the LSG-DJB group (95% CI 0.074–0.202), both lower than those in the MT group (*P* < 0.001).

DISCUSSION

The present study is the first report comparing 1 year after treatment of BS with that of MT in mildly obese type 2 diabetes mellitus patients in Japan. Verifying real-world effectiveness of BS in patients with this lower BMI range is essential to resolving the rising prevalence of diabetes in East Asian countries, which accounts for one-quarter of the global diabetes population[2]. In the USA, >40% of patients with diabetes have BMI ≥30 kg/m[2,14]. Worldwide, the majority of patients with diabetes have a BMI of <35 kg/m^2, covering >98% of the East Asian patients[15]. According to a recent cross-sectional analysis of the relationship between BMI and diabetes in 900,000 individuals in the Asian countries, the percentage of diabetes patients with a BMI of ≥35 kg/m^2 was just 0.6%, whereas those with a BMI of ≥27.5 kg/m^2 was approximately 15.3%[16].

The diabetes remission rate at the 1-year post-index date was 59.0% in the BS group, which was far better than that in the MT group (0.4%). Additionally, the rate of HbA1c <7.0% at the 1-year post-index date was 75.6% in the BS group versus 29.0% in the MT group (*P* < 0.0001), which accounted for a large proportion of HbA1c <7.0% in the BS group. These results are consistent with those of several recent randomized controlled trials with a short follow-up period, which found BS to provide better glycemic control than MT for mildly obese patients with type 2 diabetes mellitus[17–19].With respect to metabolic parameters for blood pressure, triglycerides and cholesterol, the performance improvement at the 1-year post-index date compared with the corresponding baseline level was generally better in the BS group than in the MT group. These results were similar to those in previous studies comparing BS and MT in patients with BMI <35 kg/m[2,17,20]. These showed that the risks of cardiovascular disease and cerebrovascular disease were increased due to metabolic syndrome and type 2 diabetes mellitus[21,22]. Thus, a decrease in the Framingham risk score in the BS group might reduce those risks.

The surgical methods applied to the BS group in the present study were LSG and LSG-DJB. These approaches were provided due to concerns that access to the entire stomach after laparoscopic Roux-en-Y gastric bypass would be difficult, because gastric cancer incidence is high in Japan[23]. Several investigations

Table 3 | Secondary outcomes in the matched obese patients with type 2 diabetes by treatment group

Variable	Total (*n* = 316)	BS (*n* = 78)	MT (*n* = 238)	*P*-value (independent *t*-test)
ΔHbA1c level for 1-year post-index date, (%)	*n* = 316	*n* = 78	*n* = 238	<0.0001
Mean ± SD	−0.4 ± 1.4	−1.6 ± 1.2	0.0 ± 1.2	
Median	−0.2	−1.5	0.0	
ΔBMI level for 1-year post-index date, (kg/m^2)	*n* = 316	*n* = 78	*n* = 238	<0.0001
Mean ± SD	−2.1 ± 3.5	−7.5 ± 2.8	−0.4 ± 1.3	
Median	−0.7	−7.5	−0.3	
ΔTC level for 1-year post-index date, (mg/dL)	*n* = 141	*n* = 77	*n* = 64	0.3222
Mean ± SD	−3.5 ± 40.3	−6.5 ± 44.6	0.2 ± 34.3	
Median	−2.0	−8.0	0.0	
ΔLDL-c level for 1-year post-index date, (mg/dL)	*n* = 315	*n* = 77	*n* = 238	0.0053
Mean ± SD	−2.0 ± 30.2	−10.2 ± 38.1	0.6 ± 26.8	
Median	−1.0	−12.0	1.0	
ΔHDL-c level for 1-year post-index date (mg/dL)	*n* = 315	*n* = 77	*n* = 238	<0.0001
Mean ± SD	3.1 ± 9.4	12.1 ± 12.4	0.2 ± 5.7	
Median	1.0	12.0	0.0	
ΔTG level for 1-year post-index date (mg/dL)	*n* = 315	*n* = 77	*n* = 238	<0.0001
Mean ± SD	−21.6 ± 111.3	−77.5 ± 121.7	−3.5 ± 101.6	
Median	−12.0	−53.0	−2.0	
ΔSBP level for 1-year post-index date (mmHg)	*n* = 316	*n* = 78	*n* = 238	0.0021
Mean ± SD	−3.5 ± 16.5	−10.1 ± 23.3	−1.4 ± 12.9	
Median	−2.0	−10.5	−1.0	
ΔDBP level for 1nyear post-index date (mmHg)	*n* = 316	*n* = 78	*n* = 238	0.0004
Mean ± SD	−3.0 ± 11.8	−8.7 ± 17.3	−1.1 ± 8.5	
Median	−2.0	−6.0	−1.0	
ΔFramingham score for 1- year post-index date, (point)	*n* = 141	*n* = 77	*n* = 64	0.0034
Mean ± SD	−1.0 ± 2.9	−1.6 ± 3.0	−0.1 ± 2.7	
Median	−1.0	−2.0	0.0	

BMI, body mass index; BS, bariatric surgery; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MT, medical treatment; SBP, systolic blood pressure; SD, standard difference; TC, total cholesterol; TG, triglycerides.

Table 4 | Comparison of the monthly drug treatment costs between index date and one-year post-index date for bariatric surgery group and medical treatment group

Variable ($US per patient)	BS (*n* = 78)		MT (*n* = 238)	
	Pre-index	Post-index	Pre-index	Post-index
Antidiabetic drugs				
Mean ± SD	102.9 ± 94.4	12.3 ± 30.6	52.5 ± 52.9	64.6 ± 69.1
Median	70.6	0.0	40.9	46.4
Antihypertensive drugs				
Mean ± SD	18.7 ± 24.8	5.2 ± 11.7	7.6 ± 14.2	7.5 ± 13.9
Median	2.0	0.0	2.8	2.9
Lipid-lowering drugs				
Mean ± SD	18.7 ± 25.3	6.2 ± 16.3	5.2 ± 11.8	4.9 ± 11.4
Median	14.3	0.0	1.9	0

Pre-index: for 1-month before index date. Post-index: for 1-month before 1-year post-index date. BS, bariatric surgery; MT, medical treatment; T2DM, type 2 diabetes.

have shown that LSG-DJB provides significant weight loss and improved glucose metabolism, which continue for up to 5 years comparable to laparoscopic Roux-en-Y gastric bypass[24,25].

The cost-effectiveness of BS for type 2 diabetes mellitus has been extensively investigated. Siegel *et al.* carried out a systematic literature review of studies evaluating the cost-effectiveness

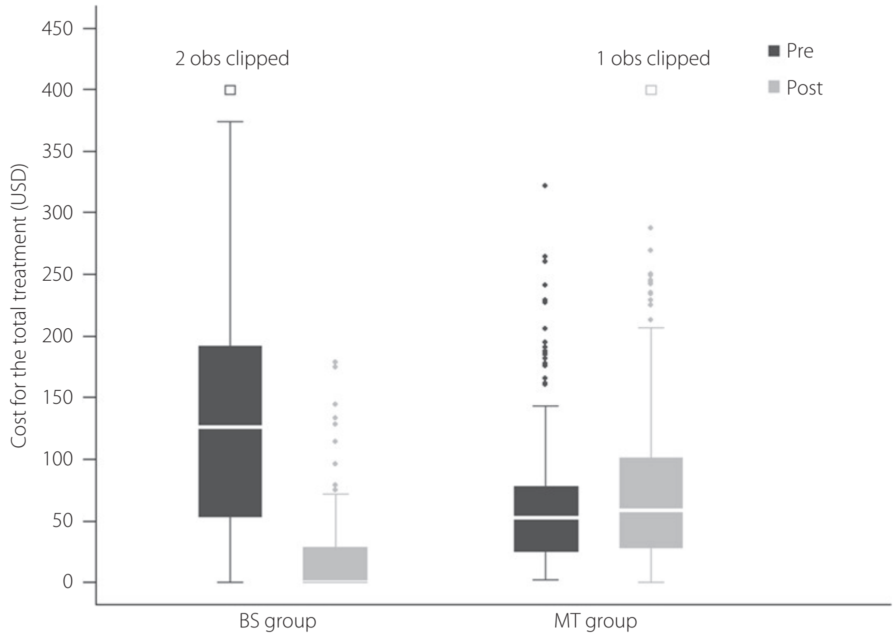

Figure 2 | The monthly drug treatment costs for metabolic diseases were compared between the index date and the 1-year post-index date. In the median comparison, the costs for the bariatric surgery (BS) group were $US0.0 for all the target drugs (antidiabetic drugs, antihypertensive drugs and lipid-lowering drugs) at the 1-year post-index date. In contrast, for the medical treatment (MT) group, the cost for those drugs increased from $US52.4 on the index date to $US58.3 at the 1-year post-index date. obs, observation; T2DM, type 2 diabetes; SD, standard difference. Pre index: for 1-month before index date. Post index: for 1 month before 1-year post-index date.

Table 5 | Logistic regression analysis for diabetes remission in obese patients with type 2 diabetes

Variable	Multivariable	
	Adjusted OR (95% CI)	*P*-value
Group		
Drug	1 (Reference)	
LSG	3,153.18 (257.26–38,647.98)	<0.001
LSG-DJB	2,121.88 (174.63–25,782.15)	<0.001
Age (years)	0.94 (0.87–1.01)	0.076
BMI level at index date (kg/m^2)	1.3 (0.91–1.86)	0.144
HbA1c level group at index date (%)		
6.5–6.9 (mild)	1 (Reference)	0.111
≥7.0	0.37 (0.11–1.25)	
Duration of type 2 diabetes		
<1 year	1 (Reference)	
≤1 and <4 years	0.93 (0.09–9.63)	0.953
≤4 and <8 years	0.62 (0.06–6)	0.682
≤8 years	0.24 (0.03–2.25)	0.212
Insulin use at 1-month pre-index date (vs no insulin use)		
No	1 (Reference)	
Yes	0.15 (0.04–0.61)	0.008

BMI, body mass index; CI, confidence interval; LSG, laparoscopic sleeve gastrectomy; LSG-DJB, laparoscopic sleeve gastrectomy with duodenojejunal bypass; MT, medical treatment; OR, odds ratio.

of diabetes management interventions. Among the American Diabetes Association-recommended interventions, BS in individuals with type 2 diabetes mellitus and obesity (BMI ≥30 kg/m^2) was categorized as cost-saving (more health benefit at a lower cost) compared with no BS ($29,641/quality-adjusted life year)[26]. Xia *et al.* carried out another meta-analysis to calculate the annual cost changes before and after surgery, and cumulative cost differences between surgical and nonsurgical groups. They found that compared with no/conventional treatment, surgery was cost saving over a lifetime scenario and, above all, medication cost savings were dominant with the proportion of medication cost change by –39.22%[27]. The financial burden of surgery is a major concern. Klein *et al.* investigated the economic impact of the clinical benefits of BS in diabetes patients with BMI ≥35 kg/m^2 using an administrative claims database of privately insured patients. They compared the patients undergoing BS with non-surgery control patients matched on demographic factors, comorbidities and healthcare costs. The overall return on investment (or cost break-even point) associated with BS was calculated, and they found that surgery costs were fully recovered after 26 months for laparoscopic surgery[28].

The cost-effectiveness in a certain country needs to be validated separately under their own healthcare system, as it differs significantly from country to country. In the present study from Japan, the drug cost for metabolic diseases (type 2 diabetes

Table 6 | Generalized linear model for the treatment cost for type 2 diabetes in the 1 month before 1-year post-index date in obese patients with type 2 diabetes

Variable	Multivariable Exp(beta) (95% CI)	*P*-value
Group		
Drug	1 (Reference)	
LSG	0.018 (0.011–0.029)	<0.001
LSG-DJB	0.016 (0.01–0.026)	<0.001
Age (years)	1.006 (0.99–1.021)	0.472
BMI level at index date (kg/m^2)	1.013 (0.95–1.079)	0.7
HbA1c level group at index date (%)		
6.5–6.9 (mild)	1 (Reference)	0.067
≥7.0	1.279 (0.984–1.662)	
Duration of type 2 diabetes		
<1 year	1 (Reference)	
≤1 and <4 years	0.926 (0.646–1.326)	0.674
≤4 and <8 years	0.846 (0.58–1.235)	0.387
≤8 years	1.211 (0.834–1.757)	0.315
Insulin use at 1-month pre-index date (vs no insulin use)	17.869 (10.568–30.217)	<0.001

Beta, regression coefficient; BMI, body mass index; CI, confidence interval; Exp, exponential; LSG, laparoscopic sleeve gastrectomy; LSG-DJB, laparoscopic sleeve gastrectomy with duodenojejunal bypass; MT, medical treatment.

Table 7 | Generalized linear model for the total treatment cost for metabolic disease (type 2 diabetes, hypertension and dyslipidemia) in the 1 month before 1-year post-index date in obese patients with type 2 diabetes

Variable	Multivariable Exp(beta) (95% CI)	*P*-value
Group		
Drug	1 (Reference)	
LSG	0.104 (0.063–0.17)	<0.001
LSG-DJB	0.122 (0.074–0.202)	<0.001
Age (years)	1.016 (1–1.033)	0.056
BMI level at index date (kg/m^2)	1.026 (0.959–1.098)	0.455
HbA1c level group at index date (%)		
6.5–6.9 (mild)	1 (Reference)	
≥7.0	1.398 (1.059–1.847)	0.019
Duration of type 2 diabetes		
<1 year	1 (Reference)	
≤1 and <4 years	0.943 (0.644–1.382)	0.765
≤4 and <8 years	0.934 (0.625–1.395)	0.737
≤8 years	1.359 (0.915–2.018)	0.13
Insulin use at 1-month pre-index date (vs no insulin use)	3.12 (1.786–5.451)	<0.001

Beta, regression coefficient; BMI, body mass index; CI, confidence interval; Exp, exponential; LSG, laparoscopic sleeve gastrectomy; LSG-DJB, laparoscopic sleeve gastrectomy with duodenojejunal bypass; MT, medical treatment.

mellitus, hypertension and dyslipidemia) decreased significantly at 1 year in the BS group, whereas there seemed to be minimal impact in the MT group. In our previous prospective study, we investigated the impact of metabolic surgery (LSG-DJB) on severe type 2 diabetes mellitus in Japanese patients with mild obesity. There was a significant reduction in the majority of medication used for glycemic control. For the patients who still required diabetes medication at 1 year after surgery, biguanide and/or dipeptidyl peptidase-4 inhibitors were the medications of choice. The use of digestive agents (proton-pump inhibitors or histamine H2-receptor antagonists blockers) increased. There was no impact of the use of psychiatric agents. The average cost of diabetes medication per patients per month significantly decreased from ¥14,635 at baseline to ¥2,567 at 1 year (82% reduction). When all medications were included in the analysis, the average cost (per patient per month) became ¥24,429 at baseline and ¥7,982 at 1 year (67% reduction)[29]. In 2014, when the cost of laparoscopic BS was not covered by the national health insurance in Japan, Kakihara *et al.*[30] evaluated the economic impact of BS by adopting the broader societal perspective considering the direct medical costs, direct non-medical costs and indirect costs. They estimated that surgery costs were fully recovered after between 18 and 32 months[30]. In the present study, the antidiabetic drug prescription rate of the MT group was 92.4%, compared with 23.1% in the BS group, even at the 1-year post-index date. Accordingly, the monthly medical expenses (median) of antidiabetic drugs increased from $US40.9 on the index date to $US46.3 at the 1-year post-index date in the MT group. In the BS group, these parameters decreased widely from $US70.6 on the index date to $US0.0 at the 1-year post-index date. Under the expectation in the future of higher prevalence of diabetes accompanied by higher treating cost, the results of the present study have presented one way to solve the problem of increasing medical costs by decreasing the prescription rate of drugs.

The present study had several limitations. First, as this study was a retrospective analysis of collected data from a database; unknown confounders, including the potential for selection biases, might affect the results. Second, MT group data were derived from the JMDC claims database, which does not include data for patients aged ≥65 years. Thus, the clinical background and demographics for the studied sample might not be extrapolated to the entire Japanese patient population. Third, not all patients in the MT group received so-called best medical treatment, as the present study used real-world data extracted from the claims database. Another limitation that might affect generalizability of results is that the BS group in the present study received surgery at a single hospital. Although the findings might not represent all Japanese type 2 diabetes mellitus patients, the clinical characteristics of this study population were compatible with those of a previous study carried out in moderately obese Asian type 2 diabetes mellitus patients in the general population[31]. Fourth, as the study period was only 1 year in duration, the long-term effects were unknown, and the relatively small sample size might have affected the results. However, Hsu *et al.* reported a 5-year follow-up comparison between BS and MT in type 2 diabetes mellitus patients with low BMI (BMI <35 kg/m^2), and found that diabetes control in the BS group was maintained during the follow-up period[31]. Fifth, drug therapy for type 2 diabetes mellitus is advancing over time, and these newer agents might not be well represented within the present study's MT cohort. For example, sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists were approved within recent years as new therapeutic agents for diabetes, and substantial therapeutic effects are expected. Finally, medical costs in the present study were limited to the drugs prescribed, which represent a fraction of the total treatment cost of diabetes. A comparison with a broader perspective is required to investigate the holistic economic impact.

Compared with medical treatment, BS effectively ameliorates glycemic control, metabolic syndrome and cardiovascular risk in mildly obese patients with type 2 diabetes mellitus. Additionally, its clinical impact might contribute to reducing drug treatment cost in Japan.

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ETHICAL INFORMATION DISCLOSURE

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