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Relationship between remission rate of type 2 diabetes and skeletal muscle after laparoscopic sleeve gastrectomy

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Abstract. Bariatric surgery can contribute to weight loss and the improvement of obesity-related diseases. Laparoscopic sleeve gastrectomy (LSG) is among the most frequently performed procedures worldwide, including in Japan. Skeletal muscle plays an essential role in energy metabolism and whole-body glucose homeostasis, and diabetes decreases insulin-induced glucose uptake in skeletal muscle. The present study investigated postoperative outcomes and factors related to type 2 diabetes (T2D) remission rates in LSG cases, including skeletal muscles. This retrospective study analyzed perioperative outcomes and factors associated with T2D remission after LSG, with a particular focus on skeletal muscle mass assessed by bioelectrical impedance analysis. LSG was performed on 90 patients between October 2016 and February 2024. First, the perioperative outcomes and weight loss effects in these 90 patients were examined. Muscle or skeletal mass perioperative factors were compared between patients with and without T2D remission. At 6 months after surgery, the median total weight loss was 21%, and the median excess weight loss was 52%. The rate of remission and improvement of T2D was 75%. The group that showed T2D remission generally had a significantly higher skeletal muscle mass or percentage throughout the preoperative and postoperative period (P<0.05). The remission rate of T2D after LSG was favorable, and a relationship was observed between T2D remission after LSG, and skeletal muscle mass before and after surgery.

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Introduction

Obesity is a common disease that is widespread around the world (1). In recent years, the incidence of obesity in Japan has rapidly increased. In 2022, the percentage of obese individuals was 31.7% for men and 21.0% for women (2). Obesity is also known to cause various diseases and to worsen prognosis (3). Bariatric surgery can contribute to weight loss and the improvement of obesity-related diseases (4). Among the various bariatric surgical techniques, laparoscopic sleeve gastrectomy (LSG) is among the most frequently performed procedures worldwide, including in Japan (5,6). In Japan, LSG was approved for insurance coverage in 2014 and is currently the most commonly performed bariatric surgical procedure. Since then, various facilities have reported on the weight loss effects of LSG and the improvement of obesity-related diseases, including type 2 diabetes (T2D) (7,8). Furthermore, predictors of diabetes remission, such as the ABCD score, have also been described (9,10).

T2D develops when environmental factors, such as aging, excessive nutritional intake, and lack of exercise, are associated with impaired insulin secretion and insulin resistance. Glucose transporter 4 (GLUT4) is important for the uptake of blood glucose into skeletal muscle cells. Insulin stimulation induces GLUT4 expression; however, this pathway is impaired in patients with diabetes. The stimulation of muscle contraction by exercise also activates GLUT4, which allows glucose uptake into the blood without insulin stimulation. In addition to obesity, skeletal muscle mass is a cause of insulin resistance (11,12).

In October 2016, at the Department of Gastroenterological Surgery II, Hokkaido University Hospital (Sapporo, Japan) introduced LSG for patients with severe obesity. Therefore, the present study investigated postoperative outcomes and factors, including skeletal muscle, associated with T2D remission rates in LSG cases performed in our department.

Materials and methods

Study population, surgical procedure and data collection. LSG was performed on 90 patients at Hokkaido University Hospital (Sapporo, Japan) between October 2016 and February

2024. At our hospital, LSG is performed for the treatment of severe obesity, in accordance with institutional criteria. The indications for LSG include: i) Patients with a body mass index (BMI) ≥35 kg/m^2 and at least one obesity-related comorbidity (type 2 diabetes, hypertension, hyperlipidemia, obstructive sleep apnea syndrome, or nonalcoholic fatty liver disease) that has not been adequately controlled by medical treatment for at least six months; or ii) patients with a BMI ≥32 kg/m^2 and <35 kg/m^2 with at least two of the above comorbidities refractory to medical treatment for at least six months. At our institution, a standardized postoperative clinical pathway is applied for patients undergoing LSG. Oral intake is initiated on postoperative day (POD) 3, and an upper gastrointestinal contrast study is routinely performed on POD 4 to confirm the absence of anastomotic leakage or obstruction. Patients are generally discharged on POD 5 or 6 when their clinical condition is stable and no postoperative complications are observed. In selected cases, discharge on POD 4 is permitted after confirmation of an uneventful postoperative course, including satisfactory findings on the contrast study, when early discharge is strongly requested by the patient.

All patients included in the present study met these criteria and were hospitalized for surgical treatment of severe obesity, not for T2D alone. T2D was evaluated as one of the obesity-related comorbidities and as a postoperative metabolic outcome.

The present study was designed as a retrospective observational study. Clinical data of these 90 patients were collected by reviewing electronic medical records at Hokkaido University Hospital. Medical records were accessed after approval by the Institutional Ethics Committee of Hokkaido University Hospital (Sapporo, Japan) and were reviewed specifically for the purpose of this study.

The study inclusion criteria were as follows: i) Patients who underwent LSG at Hokkaido University Hospital during the study period; ii) availability of complete perioperative clinical data; and iii) availability of follow-up data for at least one year after surgery, allowing evaluation of metabolic outcomes. The exclusion criteria were as follows: i) Patients with insufficient clinical or follow-up data for analysis. The data from 90 patients was analysed. First, the perioperative outcomes and weight loss effects in these 90 patients were examined. Furthermore, the patients were divided into two groups: Those in T2D remission 1 year after surgery and those in non-remission. The preoperative factors between the two groups were compared. The weight, body fat percentage, muscle mass or percentage, and skeletal muscle mass or percentage before and after surgery between the two groups were also compared. Bioelectrical impedance analysis (BIA; InBody 770; InBody, Tokyo, Japan) was used to measure muscle and skeletal muscle mass. According to the manufacturer's definitions, muscle mass represents total lean soft tissue mass, including skeletal muscle as well as non-skeletal components such as smooth muscle and other water-containing lean tissues. By contrast, skeletal muscle mass specifically refers to the mass of skeletal muscles attached to bones and involved in voluntary movement. The InBody system provided both absolute values (kg) and body-weight-adjusted percentage values for muscle mass and skeletal muscle mass. Therefore, muscle mass percentage and skeletal muscle percentage were available for all patients and were used for longitudinal comparisons in this study. The present study was approved (approval no. C-T2023-0412) by the Institutional Ethics Committee of Hokkaido University Hospital.

The amount of blood loss was estimated from the amount of blood aspirated during surgery. Cases with 0 ml indicate that the amount was so small that it could not be counted. T2D was diagnosed according to established clinical guidelines. Patients were defined as having T2D if they met at least one of the following criteria: Fasting plasma glucose ≥126 mg/dl, HbA1c ≥6.5%, or 2-h plasma glucose ≥200 mg/dl during an oral glucose tolerance test. Patients with a prior clinical diagnosis of T2D were also included, regardless of whether they were receiving pharmacological treatment at the time of surgery. T2D remission was defined as the maintenance of HbA1c <6.5% for at least 3 months without antidiabetic medication, in accordance with the international consensus report on the definition of remission in T2D (13). According to this consensus, a minimum duration of 3 months after cessation of glucose-lowering therapy is required to confirm remission. In the present study, remission status was assessed at 1 year after surgery, allowing sufficient postoperative follow-up to evaluate glycemic outcomes. Hypertension remission was defined as normalization of blood pressure (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg) maintained after discontinuation of medical treatment (14). Dyslipidaemia remission was defined as normalized cholesterol level (T-cholesterol <200 mg/dl, LDL-cholesterol <120 mg/dl, HDL-cholesterol >40 mg/dl) maintained after discontinuation of medical treatment (15). T2D, hypertension and dyslipidaemia improvement refer to cases in which a reduction in drug use was feasible.

Statistical analysis. Quantitative data were expressed as medians and ranges. Friedman's test was used to compare pre- and post-operative weight and BMI. For subsequent post-hoc analysis, the Nemenyi post hoc test was employed to identify specific differences between group pairs. Differences between groups were compared using the Wilcoxon rank sum test. Univariate analyses were performed using logistic regression models. Multivariate logistic regression analyses were additionally performed to explore independent factors associated with T2D remission, including age, duration of diabetes, baseline HbA1c, and body composition parameters. Variables showing strong correlations were carefully evaluated to avoid multicollinearity. Receiver operating characteristic (ROC) curve analyses were performed for each continuous variable using the entire cohort of 90 patients, with T2D remission as the binary outcome. Optimal cut-off values were determined by maximizing the Youden index (Fig. S1), and these values were used to dichotomize variables for the analyses shown in Table III. Statistical significance was set at P<0.05. All analyses were performed using JMP Pro® 17 software (SAS Institute Inc.).

Results

The characteristics of the patients in the present study are presented in Table I. The median age was 44 years (range, 27-65 years), and the proportion of women (53 cases) was

Table I. Clinical characteristics of patients who underwent laparoscopic sleeve gastrectomy.

Characteristics	Patients (n=90)
Age (years)[a]	44 (27-65)
Sex (male/female)	37/53
Weight at first visit (kg)[a]	118 (79-194)
BMI at first visit (kg/m^2)[a]	43 (31.7-64.3)
Complications	56 (62.2%)
T2D	56 (62.2%)
Use of one oral antidiabetic drug	24 (26.7%)
Use of two or more antidiabetic drugs	18 (20.0%)
Use of insulin	11 (12.2%)
Hypertension	62 (68.9%)
Dyslipidaemia	49 (54.4%)
Sleep apnoea syndrome	70 (77.8%)

[a]Median (range). The total number of patients with T2D includes individuals with untreated T2D diagnosed according to standard clinical criteria. BMI, body mass index; T2D, type 2 diabetes.

Table II. Perioperative clinical outcomes of laparoscopic sleeve gastrectomy.

Parameter	Patients (n=90)
Operation time (min)[a]	150 (96-277)
Blood loss (ml)[a]	0 (0-50)
Open conversion	0
Postoperative complications (CD grade ≥II)[b]	5 (5.5%)
Intraperitoneal bleeding	3
Rectus abdominis hematoma	1
Delayed gastric emptying	1
Re-operation	1 (1.1%)
Postoperative hospital stay (days)[a]	6 (4-12)

[a]Median (range); [b]CD grade, Clavien-Dindo classification grade.

slightly higher than that of men. The median weight at the first visit was 118 kg (range, 79-194 kg), and the median body mass index (BMI) was 43 kg/m^2. Among the 90 patients included in the present study study, 6 patients (6.7%) had a preoperative BMI between 32 and 35 kg/m^2. These patients met the institutional eligibility criterion for metabolic/bariatric surgery corresponding to BMI ≥32 kg/m^2 and <35 kg/m^2 with two or more obesity-related comorbidities refractory to medical treatment, and were included as part of the consecutive LSG cohort. Obesity-related diseases, such as T2D (62.2%), hypertension (68.9%), dyslipidaemia (54.4%), and sleep apnoea syndrome (77.8%) were present in ~60% of the patients. Among patients with T2D, 24 (26.7%) were using one antidiabetic drug, 18 (20.0%) were using two or more antidiabetic drugs, 11 (12.2%) were using insulin, and 3 (5.3%) received only dietary therapy. The perioperative data of the patients are shown in Table II. The median operative time was 150 min (range, 96-277 min), and blood loss was generally minimal. Complications, defined as Clavien-Dindo postoperative complication classification grade (CD grade) II or higher (16) was observed in five cases (5.5%), one of which had CD grade III complications. This patient required reoperation due to intraperitoneal bleeding. No cases of conversion to open surgery were observed, and the median postoperative hospital stay was 6 days (range, 4-12 days). Among the patients with a postoperative hospital stay of 4 days, no postoperative complications were observed, and early discharge was allowed based on stable clinical findings and the preference of the patient. The changes in weight and BMI after surgery are shown in Fig. 1. The peak postoperative weight loss occurred at 6 months after surgery, while the peak decrease in BMI was observed at 12 months postoperatively. Significant differences were observed in weight and BMI at all post-operative time-points compared with the pre-operative baseline. The median peak total weight loss was 21% at 6 months after surgery, and the median peak excess weight loss was 52% at 6 months after surgery. Subsequently, the condition remained largely stable for ~2 years after surgery. Regarding the rate of improvement in obesity-related diseases, hypertension and dyslipidaemia improved in ~50% of the patients. T2D was in remission in ~60% of cases, and increasing to 75% when improvement was included.

The patients were divided into two groups: Those in T2D remission 1 year after surgery (remission group) and those in non-remission (non-remission group). The remission group included 35 patients and the non-remission group included 16 (Fig. 2). Of note, 5 patients were excluded because their postoperative follow-up period was <1 year. The preoperative data of the patients in the two groups are shown in Table III. Absolute skeletal muscle mass (kg) was included as one of the variables in the univariate analysis; in addition, skeletal muscle percentage, a body-size-adjusted index, was analyzed in the longitudinal postoperative comparisons. Factors that showed significant differences in the univariate analyses were duration of treatment for T2D [odds ratio (OR)=3.723; 95% CI, 1.056-13.125; P=0.0409)], body fat percentage (OR=4.814; 95% CI, 1.359-17.050; P=0.0148), muscle mass (OR=7.333; 95% CI, 1.754-30.656; P=0.0063), and skeletal muscle mass (OR=6.355; 95% CI, 1.730-23.339; P=0.0053). In multivariate logistic regression analyses adjusting for established clinical factors, skeletal muscle mass did not remain a statistically significant independent predictor of T2D remission. Therefore, skeletal muscle mass was not included as an independent variable in the final multivariate model. When the changes in postoperative muscle or skeletal muscle mass between the two groups were also examined, the results showed that the remission group generally had significantly higher muscle and skeletal muscle masses (P<0.05; Fig. 3). For muscle percentage, a significant difference (P<0.05) was observed only 3 months after surgery. However, in skeletal muscle percentage, a significant difference (P<0.05) was observed at 3, 6, and 12 months after surgery. The patients in the remission group tended to have a significantly higher skeletal muscle percentage.

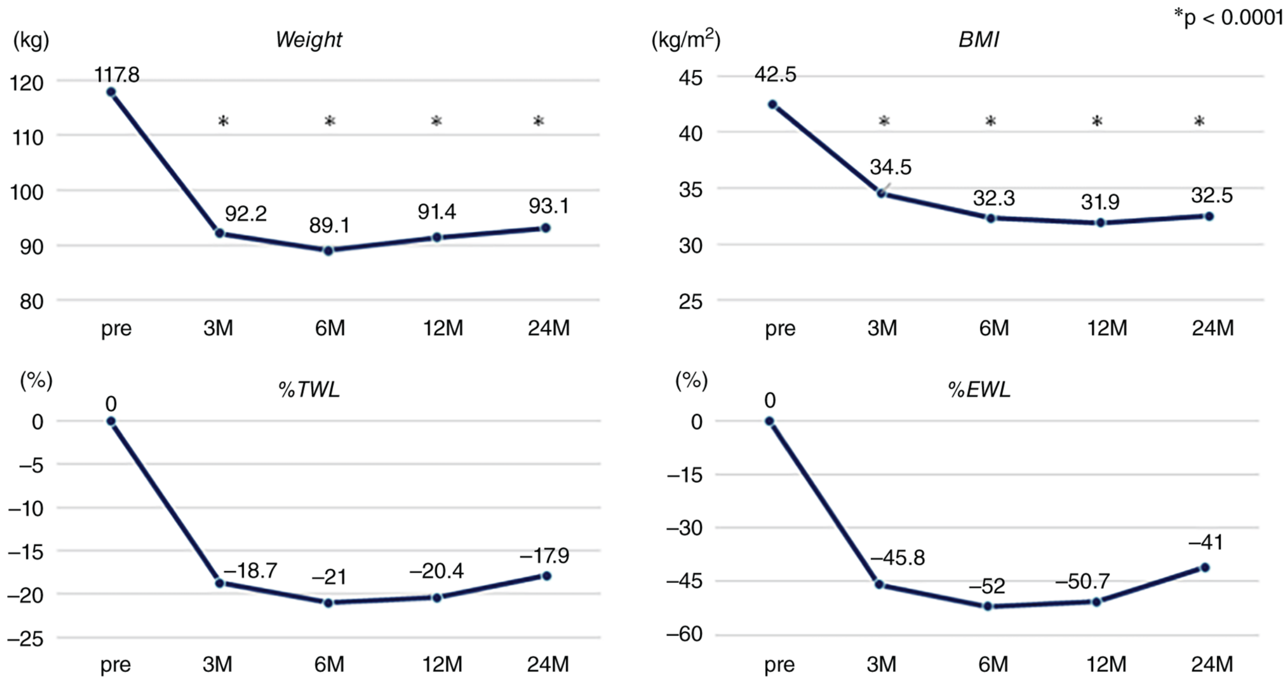

Figure 1. Trends in weight and BMI and rate of weight loss after laparoscopic sleeve gastrectomy. Values are presented as medians. *P<0.0001. BMI, body mass index; %TWL, total weight loss rate; %EWL, excess weight loss rate; pre, pre-surgery; M, months.

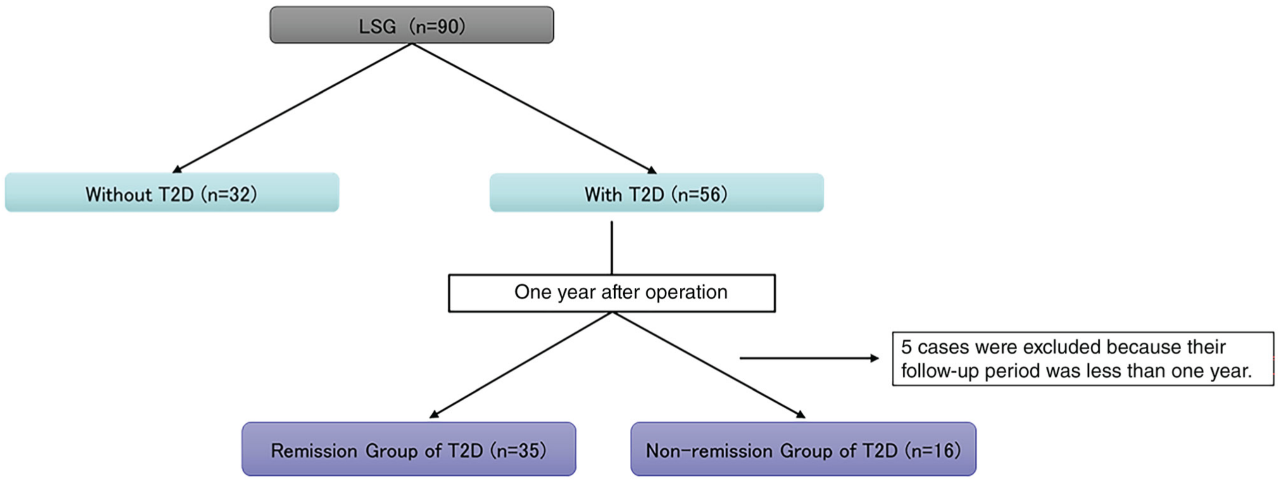

Figure 2. Grouping of the study participants. The participants were divided according to whether they achieved T2D remission or not (non-remission group). T2D, type 2 diabetes.

Discussion

For severe obesity, dietary, exercise, cognitive behavioural, and pharmacological therapies have been used. However, these treatments are often ineffective, and surgical intervention is frequently necessary (17). Bariatric surgery such as LSG is effective for weight loss and for improving metabolism (18,19). In addition to LSG, various other procedures, such as adjustable gastric banding and biliopancreatic diversion, are used in bariatric surgery. LSG is currently the most commonly performed procedure worldwide (5). In the United States and elsewhere, the weight loss effect of LSG is greater than that of medical treatments (8). The results of a multicentre study have also been reported in Japan (19). According to this study, the total weight loss rate (%TWL) and excess weight loss rate (%EWL) 1 year after LSG were 29 and 59%, respectively. In the present study, the %TWL and %EWL 1 year after LSG were 20.4 and 50.7%, respectively. Although the number of cases was small, the effect of weight loss was comparable to that reported in previous studies.

Obesity is associated with a high incidence of diseases such as T2D, hypertension, and dyslipidaemia. Obesity-related diseases can be improved with LSG. Saiki *et al* (20) reported that the improvement rates of hypertension and dyslipidaemia were 41.8 and 59.7%, respectively, after LSG. In the present study, the improvement rates of hypertension and dyslipidaemia were 50 and 51%, respectively. These results are comparable with those of previous reports (7,8). In Japan, the number of

Table III. Preoperative factors associated with T2D remission.

Parameter	Remission of T2DM (n=35)	Non-remission of T2DM (n=16)	Univariate analysis OR	Univariate analysis 95% CI	Univariate analysis P-value	Multivariate analysis OR	Multivariate analysis 95% CI	Multivariate analysis P-value
Age (years) (≥42/<42)	18/17	13/3	4.092	0.989-16.925	0.0517			
Sex (female/male)	16/19	11/5	2.612	0.749-9.108	0.1318			
Weight (kg) (<120/≥120)	16/19	12/4	3.562	0.958-13.236	0.0578			
BMI (kg/m^2) (≤43/>43)	19/16	11/5	2.329	0.668-8.112	0.1841			
HbA1c (%) (≥7.2/<7.2)	8/27	6/10	2.025	0.561-7.307	0.2812			
mABCD score (≤5/>5)	16/19	12/4	3.562	0.958-13.236	0.0578			
Duration of treatment of T2D (year) (≥7.0/<7.0)	13/22	11/5	3.723	1.056-13.125	0.0409[a]	4.031	0.911-21.163	0.0664
History of insulin use (Yes/No)	5/30	5/11	2.727	0.659-11.272	0.1658			
Body fat percentage (%) (≥50/<50)	9/26	10/6	4.814	1.359-17.050	0.0148[a]	4.661	1.097-23.061	0.0368[a]
Muscle mass (kg) (<55/≥55)	13/22	13/3	7.333	1.754-30.656	0.0063[a]	1.449	0.123-14.316	0.7530
Skeletal muscle mass (kg) (≤30/>30)	9/26	11/5	6.355	1.730-23.339	0.0053[a]	4.091	0.534-43.776	0.1784

[a]P<0.05. OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; T2D, type 2 diabetes.

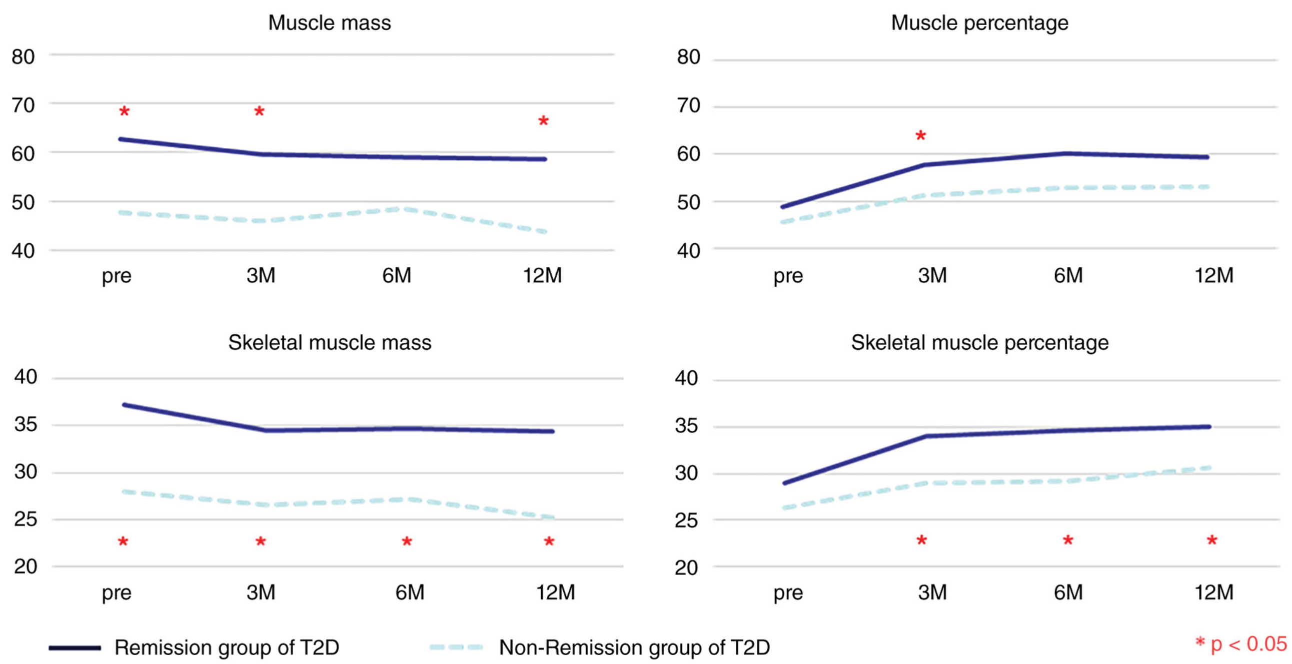

Figure 3. Trends in muscle mass/percentage and skeletal muscle mass/percentage after laparoscopic sleeve gastrectomy. *P<0.05. T2D, type 2 diabetes; pre, pre-surgery; M, months.

patients with obesity and T2D is rapidly increasing, which is similar to trends reported in other countries. In Asian patients, T2D tends to become severe at relatively low BMI (21,22). Therefore, more attention should be paid to bariatric surgery as a treatment for T2D. The improvement rate of T2D with LSG alone is 75% (20), and this study showed similar results. However, some cases where LSG alone does not result in remission of T2D occur (19,23). Lee *et al* (10) reported the ABCD score calculated from the age, BMI, preoperative serum C-peptide immunoreactivity, and duration of diabetes of the patient, is predictive of T2D remission after bariatric surgery including LSG (10). In Japan, Naitoh *et al* (24) also reported that sleeve gastrectomy with duodenal-jejunal bypass, which combines LSG with bilio-pancreatic diversion and duodenal switch, improves the rate of diabetes remission in cases with an ABCD score ≤5 (24). Our study did not show a significant difference between the ABCD score and T2D remission rate (P=0.0511); however, a tendency for a lower remission rate in cases with an ABCD score ≤5 was observed. These results suggest that a significant difference may emerge with a larger number of cases.

Although skeletal muscle mass did not remain a statistically significant independent predictor in multivariate analysis after adjustment for established clinical factors, it demonstrated a strong and consistent association with T2D remission in univariate analyses and during postoperative follow-up. This finding suggests that skeletal muscle mass may influence glycemic outcomes indirectly rather than acting as an isolated determinant. The lack of independent significance may be attributable to collinearity with other metabolic or anthropometric factors, as well as the relatively small sample size. Therefore, skeletal muscle mass should be interpreted as an important contributory factor within a multifactorial mechanism underlying T2D remission after LSG, rather than as a sole independent predictor.

Furthermore, the relationship between diabetes and skeletal muscle was examined. Skeletal muscle plays an essential role in energy metabolism and whole-body glucose homeostasis (25,26). In addition to GLUT4, some studies have shown that PGC-1α, which is highly expressed in skeletal muscle, improves insulin sensitivity in diabetic model mice, and the protein irisin, which is related to PGC-1α, prevents the onset of diabetes (27,28). Skeletal muscles process glucose in the blood through muscle contractions induced by exercise. The comprehensive treatment for patients with obesity includes exercise therapy, which reduces the risk of developing T2D (29). This suggests a close relationship between diabetes, skeletal muscle mass, and exercise. Regarding the relationship between bariatric surgery and skeletal muscle, Jassil *et al* (30) recently reported that bariatric surgery resulted in comparable weight loss, changes in body composition, and improvements in relative muscle strength and physical function. However, no study has investigated the relationship between the remission rate of T2D and skeletal muscle mass after bariatric surgery. In the present study, univariate analysis showed that muscle mass and skeletal muscle mass were higher in patients with T2D remission. Associations were confirmed between the remission rate of T2D and muscle mass or percentage and skeletal muscle mass or percentage before and after surgery. The mechanism is unclear; however, the results suggest that management focusing on skeletal muscle during the perioperative period is important when performing LSG. A previous study on sarcopenia showed that resistance exercise contributes to increases in muscle mass (31).

Recent studies have also highlighted the significance of body composition in glucose metabolism (32,33). Nguyen *et al* (34) reported that gains in fat-free mass and skeletal muscle mass following LSG are positively associated with T2D remission. These findings align with our results, which show that higher skeletal muscle mass is a favorable factor for postoperative glycemic control. However, our study presents several distinct findings compared to these reports. While Nguyen *et al* (34) emphasized that muscle mass gain is significantly associated with T2D remission only in males, our data suggests that skeletal muscle mass is a significant predictor for the entire Japanese cohort regardless of sex. Furthermore, unlike the study by Nguyen *et al* (34), which focused on the 'gain' of muscle mass postoperatively, our results emphasize the importance of 'preoperative' skeletal muscle mass storage. This suggests that maintaining a high initial muscle mass may be a key factor for successful remission in Japanese patients, who generally have a lower BMI compared with Western or other Asian populations.

The present study had some limitations. It had a retrospective design and included a few cases and only patients with short observation periods were included in the study. Although remission was defined based on a minimum duration of 3 months, as recommended by the international consensus, longer-term follow-up is important to confirm the durability of diabetes remission. Further studies with extended observation periods are warranted. Skeletal muscle mass was assessed using BIA (InBody). Although BIA is a widely used and non-invasive method, its measurements can be influenced by hydration status and fluid shifts. This limitation is particularly relevant in the early postoperative period after LSG, and postoperative skeletal muscle data should therefore be interpreted with caution. Skeletal muscle mass is influenced by physical activity, including exercise habits and daily activity levels. However, detailed information on physical activity or rehabilitation interventions was not available in this retrospective study. Therefore, the potential confounding effect of physical activity on skeletal muscle mass and T2D remission cannot be fully excluded. Absolute skeletal muscle mass (kg) is influenced by body size and body weight, which may limit its clinical interpretability when used alone. Although absolute values were included in the univariate analysis, skeletal muscle percentage, a body-size-adjusted index, was also evaluated and showed consistent differences between the remission and non-remission groups. Therefore, findings based on absolute skeletal muscle mass should be interpreted with caution. In the future, the sample size should be increased and the long-term outcomes should be observed. Moreover, it is important to elucidate through basic research the changes in muscle mass and GLUT4 expression that take place during rehabilitation.

In conclusion, the remission rate of T2D after LSG was favorable; however, cases in which remission was not achieved occurred. In the present study, the relationship between the T2D remission rate in LSG and skeletal muscle mass or percentage before and after surgery was demonstrated. It is suggested that perioperative management, including preoperative rehabilitation focusing on skeletal muscle, is important for improving the T2D remission rate in LSG. Expanded clinical data and basic research are required to elucidate the mechanism underlying T2D improvement.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors (HT, YE, YO, HW, TN, AN, TS and SH) contributed to the study conception and design. HT, YE and SH performed the material preparation, data collection and analysis. HT and YE confirm the authenticity of all the raw data. HT and YE wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. C-T2023-0412) by the Institutional Ethics Committee of the Hokkaido University Hospital (Sapporo, Japan).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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