Effect of Conventional Medical Therapy or Laparoscopic Sleeve Gastrectomy on Urinary Albumin in Japanese Subjects with Severe Obesity: An Observational Study

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Keywords
Obesity · Conventional medical therapy · Sleeve gastrectomy · Albuminuria

Abstract

Introduction: In patients with severe obesity, albuminuria can be improved by both conventional medical therapy and bariatric surgery. The purpose of this study was to compare the impact of weight loss achieved through conventional medical therapy or laparoscopic sleeve gastrectomy (LSG) on albuminuria in Japanese subjects with severe obesity and identify the factors involved. Methods: We retrospectively evaluated the clinical characteristics including the urinary albumin/creatinine ratio (UACR) of 340 consecutive subjects with a body mass index \( \geq 35 \) who received LSG (\( n = 242 \)) or medical therapy (\( n = 98 \)) between 2010 and 2018 and were followed for at least 12 months. Results: The baseline of the UACR was not different between the 2 groups. At the 12-month follow-up, total weight loss (TWL) and decreases in glycosylated hemoglobin (HbA1c) and \( \log_e \) UACR were greater in the LSG group than in the medical therapy group (body weight; −35.7 kg vs. −8.0 kg, \( p < 0.001 \), HbA1c; −1.4% vs. −0.7%, \( p < 0.001 \), \( \log_e \) UACR; −0.3 vs. 0.9, \( p < 0.001 \)). The rate of complete remission of diabetes was significantly higher in the LSG group than in the medical therapy group. At 12 and 36 months (\( n = 111 \) in the medical therapy group, \( n = 56 \) in the LSG group at 36 months), \( \log_e \) UACR increased in the medical therapy group, while it remained unchanged or decreased in the LSG group. In subjects with microalbuminuria and macroalbuminuria, changes in the \( \log_e \) UACR correlated with percent total body weight loss (%TWL) in both groups at 12 months. Percent TWL contributed independently to the change in the \( \log_e \) UACR, irrespective of whether LSG was performed. In receiver-operating characteristic analysis, a weight loss of 7.8% predicted a decrease in the UACR (\( \Delta \)UACR < 0 at 12 months). Conclusion: Our analysis suggests that albuminuria may increase over time if only medical therapy is continued. To improve albuminuria, weight loss may be more important than whether LSG is performed.

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Introduction

Obesity is an independent risk factor for chronic kidney disease as well as cardiovascular diseases [1–3]. Albuminuria and proteinuria associated with severe obesity are often caused by various factors related to obesity, such as diabetes, hypertension, and dyslipidemia. Obesity-related glomerulopathy (ORG) has recently attracted attention as renal damage caused by obesity [4, 5]. The main clinical course of ORG is the increase in glomerular filtration rate and an increase in intraglomerular pressure followed by the appearance of proteinuria.

In patients with severe obesity, albuminuria can be improved by both conventional medical therapy and bariatric surgery [6–8]. The mechanism of improvement of albuminuria by bariatric surgery has been suggested to be not only weight loss but also the improvement of systemic inflammation and promotion of podocyte differentiation [9, 10]. In the Swedish Obese Subjects study, an ongoing prospective, controlled intervention study, bariatric surgery improved albuminuria more than medical therapy [8], while medical therapy was associated with a higher incidence of albuminuria in long-term follow-up [11]. However, these studies did not include sleeve gastrectomy (SG), a form of bariatric surgery.

In Japan, laparoscopic SG (LSG) is a commonly selected modality of bariatric surgery, partly because of health-care insurance coverage [12]. Although several studies have examined whether LSG improves albuminuria in severely obese subjects [13, 14], the effect of LSG alone on albuminuria in Japanese patients with severe obesity compared with medical therapy is unknown. In addition, the factors that contribute to the variability of albuminuria are also unclear. The purpose of this study was to compare the impact of weight loss achieved through conventional medical therapy or LSG on albuminuria in Japanese subjects with severe obesity and identify the factors involved.

Materials and Methods

Study Subjects

In the present study, we retrospectively reviewed the clinical data recorded at the Toho University Sakura Medical Center between July 2010 and January 2018 to identify subjects who were treated for obesity (body mass index [BMI] ≥35 kg/m²) by LSG or conventional medical therapy and were followed for at least 12 months. In Japan, LSG is covered by health-care insurance for patients with obesity with a BMI ≥35 kg/m² and one or more of the following conditions: diabetes, hypertension, dyslipidemia, or obstructive sleep apnea syndrome. A total of 340 subjects were identified, 98 of whom received LSG and 242 received medical therapy. Subjects, especially those in the medical therapy group, had interrupted their hospital visits at 36 months. Hundred and thirty-one out of 242 subjects in the medical therapy group had either stopped visiting the hospital or were still visiting the hospital but had not been seen at 36 months. In the LSG group, 16 out of 98 subjects had stopped visiting the hospital, and 26 patients had not passed 36 months postoperatively at the time of writing this article.

Subjects in the medical therapy group were prescribed a diet of 20–25 kcal/kg of ideal body weight (BW) per day and antihyperglycemic agents aiming to maintain glycylated hemoglobin (HbA1c) at <7%. Subjects in the LSG group received the same prescriptions as for patients in the medical therapy group preoperatively and postoperatively. None of the subjects underwent renal biopsy for diagnosing nephropathy.

We compared the following parameters before and 12 and 36 months after LSG or before and 12 and 36 months after initiation of medical therapy: BW, BMI, serum creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), HbA1c, systolic and diastolic blood pressure, and urinary albumin/creatinine ratio (UACR). The serum LDL-C level was calculated using the Friedewald formula. The eGFR was calculated using the estimation formula adopted by the Japanese Society of Nephrology, which is based on serum creatinine level, gender, and age [15, 16].

Fasting blood and urine samples were collected at baseline (0 months) and 12 months and 36 months after initiating medical therapy or after LSG (baseline, at 12 months and at 36 months, respectively, hereinafter). Urinalysis was performed using spot urine samples during hospital visits. The UACR was determined using a turbidimetric immunoassay (LSI Medience Corporation, Itabashi-ku, Japan). Although 24-h urine collection is the golden standard for the evaluation of albuminuria, the UACR also correlates relatively well with 24-h urine collection [17–19], and we used the UACR in this study.

Diabetes was diagnosed according to the diagnostic criteria of the Japan Diabetes Society [20], hypertension according to the Japanese Society of Hypertension [21], and dyslipidemia according to the Japan Atherosclerosis Society [22]. Complete remission of diabetes was defined as HbA1c <6.0% without using any diabetes medication [23]. Normal albuminuria was defined as UACR <30 mg/gCr, microalbuminuria as 30–299 mg/gCr, and macroalbuminuria as 300 mg/gCr or more.

Statistical Analysis

Data are expressed as means ± SD or median (interquartile range) as appropriate. Normal distribution was tested using the Shapiro-Wilk test. Parametric data were analyzed using Student’s t test and nonparametric data using the Wilcoxon signed-rank test (paired) and Wilcoxon rank-sum test (unpaired). Fisher’s exact test was used to detect significant differences between proportions and categorical variables. Simple linear regression analysis was performed by Spearman’s rank correlation coefficient. Multiple regression analysis was performed to identify parameters contributing to the decrease in the UACR. Sensitivity and specificity with respect to the decrease in the UACR (AUACR <0 at 12 months) were analyzed using conventional receiver-operating characteristic (ROC) curves. The cutoff level of ROC curves was set using...
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Youden’s index. These analyses were performed using SPSS software version 26 (Armonk, NY, USA: IBM Corp). *p values <0.05 were considered significant.

Results

Baseline Characteristics of the Medical Therapy Group and the LSG Group

Table 1 shows the baseline characteristics of the medical therapy and the LSG groups. The mean age, BMI, FBG, and HbA1c were not significantly different between the 2 groups. The rate of diabetes, hypertension, and dyslipidemia was not significantly different between the 2 groups. The number of anti-lipidemic drugs used was slightly higher in the LSG group. There was no difference in the UACR at baseline, but when divided into subjects with and without diabetes, the UACR was higher in the medical therapy group than in the LSG group. When examined only within the medical therapy group, subjects with diabetes had a higher UACR than subjects without diabetes. The rate of normal/micro/macronalbuminuria was also significantly different between the 2 groups.

Changes in Clinical Parameters after 12 and 36 Months

At 12 months, BW, BMI, FBG, and HbA1c decreased significantly, and HDL-C increased significantly compared with baseline in both groups (Table 2). In the medical therapy group only, the eGFR decreased, while the
UACR and logₑ UACR increased. On the other hand, in the LSG group only, TG and LDL-C decreased. At 36 months, BW, BMI, eGFR, and HbA1c decreased significantly and HDL-C increased compared with baseline in both groups. Uric acid decreased, while the logₑ UACR increased only in the medical therapy group, whereas TG, FBG, and logₑ UACR decreased only in the LSG group.

Comparing the changes from baseline in clinical and laboratory parameters at 12 months between the medical therapy group and LSG group (Table 2), percent total BW loss (%TWL) and the decreases in BW, BMI, TG, FBG, HbA1c, and logₑ UACR and the increase in HDL in the LSG group were significantly greater than the changes in the medical therapy group. The rate of complete remission of diabetes was significantly higher in the LSG group than in the medical therapy group. At 36 months, %TWL and the decreases in BW, BMI, triglyceride, FBG, HbA1c, and logₑ UACR and the increase in HDL-C were significantly greater in the LSG group than the changes in the medical therapy group. When divided into subjects with and without diabetes, the UACR and logₑ UACR in the medical therapy group at 12 and 36 months. No significant difference in ΔUACR and Δlogₑ UACR in the LSG group at 12 and ΔUACR at 36 months).

Table 2. Changes in clinical parameters at 12 and 36 months

| Parameter                        | At 12 months (vs. baseline) | At 36 months (vs. baseline) |
|----------------------------------|-----------------------------|----------------------------|
|                                 | medical therapy (n = 242)   | LSG (n = 98)               | medical therapy (n = 111) | LSG (n = 56)               |
|                                 | p value                     | p value                    |
| ∆BW, kg                         | −8.0±12.9††                 | −35.7±17.0††               | −7.8±15.3††               | −29.2±18.3††               | 0.000*                    |
| ∆BMI, kg/m²                      | −2.9±4.6††                 | −13.0±5.9††               | −2.9±5.8††               | −10.6±6.5††               | 0.000*                    |
| ∆%TWL, %                        | 6.4±9.9                     | 28.6±10.5                 | 0.000*                    | 6.2±11.2                   | 23.2±12.3                 | 0.000*                    |
| ∆Creatinine, mg/dL              | 0.0±0.2                     | 0.0±0.2                   | 0.538                     | 0.0±0.2                    | 0.0±0.2                   | 0.121                     |
| ∆eGFR, mL/min/1.73m²             | −3.1±14.4††                 | −1.5±17.1                 | 0.385                     | −5.7±15.2††               | −7.1±18.2††               | 0.616                     |
| ∆Uric acid, mg/dL               | −0.1±1.3                    | 1.9±24.1                 | 0.431                     | −0.3±1.3                  | −0.3±1.5                  | 0.989                     |
| ∆TC, mg/dL                      | 3.0±36.6                    | 0.2±41.4                 | 0.565                     | 2.2±44.3                  | 6.4±47.3                  | 0.573                     |
| ∆TG, mg/dL                      | −3.4±170.8                  | −98.3±116.4††             | 0.000*                    | −1.6±280.6                | −85.1±100.3††             | 0.032*                    |
| ∆HDL-C, mg/dL                   | 4.3±24.6††                  | 14.6±13.8††               | 0.000*                    | 3.5±9.6††                 | 13.3±13.5††               | 0.009*                    |
| ∆LDL-C, mg/dL                   | −0.6±40.3                   | −7.8±36.8†                | 0.135                     | −1.0±40.2                 | −2.7±39.6                 | 0.800                     |
| ∆FBG, mg/dL                     | −15.9±85.4††                | −46.6±61.0††              | 0.002*                    | −7.1±87.8                 | −41.0±53.6††              | 0.009*                    |
| ∆HbA1c, %                       | −0.7±1.6††                  | −1.4±1.7††                | 0.000*                    | −0.6±2.0††                | −1.3±1.8††                | 0.033*                    |
| ∆UACR in all subjects, mg/gCr   | 128.2±714.1††               | −28.2±146.7               | 0.003*                    | 137.6±730.7               | −31.5±144.2               | 0.034*                    |
| In subjects with diabetes        | 148.1±740.4††               | −51.7±183.0               | 0.004*                    | 126.6±724.2               | −43.8±181.0               | 0.291                     |
| In subjects without diabetes     | 88.9±662.3                  | 6.6±48.9                 | 0.544                     | 161.7±756.9               | −10.0±10.3††              | 0.224                     |
| ∆Logₑ UACR in all subjects, logₑ UACR | 0.9±1.9††                  | −0.3±1.0                 | 0.000*                    | 1.3±1.5††                 | −0.4±0.9††               | 0.000*                    |
| In subjects with diabetes        | 0.8±1.7††                   | −0.3±1.1                 | 0.001*                    | 1.0±1.2††                 | −0.0±0.9                 | 0.002*                    |
| In subjects without diabetes     | 1.2±2.4                     | −0.3±0.9                 | 0.031*                    | 1.9±2.0†                  | −0.9±0.8††,§              | 0.005*                    |
| ∆Systolic BP, mm Hg              | 1.0±27.9                    | −4.1±24.0                | 0.316                     | −5.9±16.3                 | −0.9±18.5                 | 0.339                     |
| ∆Diastolic BP, mm Hg             | 0.6±16.0                    | 0.8±15.3                 | 0.958                     | −3.4±13.9                 | −2.4±25.0                 | 0.885                     |
| Rate of CR of diabetes, %        | 41.9                        | 77.4                     | 0.000                     | 36.9                      | 50.9                      | 0.092                     |

Data are presented as means ± SD (other than ΔUACR) and as means ± SEM (ΔUACR). %TWL, percent total body weight loss; CR, complete remission; SEM, standard error of the mean; LSG, laparoscopic sleeve gastrectomy; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; UACR, urinary albumin/creatinine ratio; BP, blood pressure; BW, body weight. ∆ denotes the change from baseline. CR of diabetes was defined as HbA1c <6.0% without using any diabetes medication. † p < 0.05. †† p < 0.01, versus baseline in each group. * Significant difference between the medical therapy group and LSG group. § Significant difference in ∆logₑ UACR when compared by the presence of diabetes in the LSG group at 36 months (no significant difference in ΔUACR and Δlogₑ UACR in the medical therapy group at 12 and 36 months. No significant difference in ∆UACR and ∆logₑ UACR in the LSG group at 12 and ΔUACR at 36 months).
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Changes in the Mean UACR and Loge UACR from Baseline until 36 Months

The changes in the UACR and loge UACR over time in the medical therapy group and the LSG groups, respectively, were examined (Fig. 1). The medical therapy group showed a significant increase of the UACR compared to baseline at 12 months, while the LSG group showed no change until 36 months. For the loge UACR, a significant increase compared to baseline was observed at both 12 and 36 months in the medical therapy group, while a significant decrease was found at 36 months in the LSG group.

Relationship between Changes in the Loge UACR and %TWL by Medical Therapy or LSG

Figure 2 shows the correlation between %TWL and the change in the loge UACR (Δloge UACR) at 12 months in subjects with microalbuminuria or macroalbuminuria. UACR, urinary albumin/creatinine ratio; LSG, laparoscopic sleeve gastrectomy; %TWL, percent total body weight loss; \( r_s \), Spearman’s rank correlation coefficient.

**Fig. 1.** Changes over time in the mean UACR and loge UACR from baseline to 12 and 36 months in the medical therapy group and LSG group. Data are presented as means ± SEM for the mean UACR and as means ± SD for the loge UACR. † \( p < 0.05 \), †† \( p < 0.01 \), NS, not significant; versus, baseline in each group. UACR, urinary albumin/creatinine ratio; LSG, laparoscopic sleeve gastrectomy.

**Fig. 2.** Relationship between changes in the loge UACR and %TWL in the medical therapy group and LSG group in subjects with microalbuminuria or macroalbuminuria. UACR, urinary albumin/creatinine ratio; LSG, laparoscopic sleeve gastrectomy; %TWL, percent total body weight loss; \( r_s \), Spearman’s rank correlation coefficient.
subjects with microalbuminuria or macroalbuminuria in the medical therapy group and LSG group. Since 63.5% of the subjects in the medical therapy group and 80.3% in the LSG group had normal albuminuria at baseline, the number of subjects in this part of the analysis was limited. However, a significant negative correction between %TWL and ∆log e UACR was observed in both groups. In subjects with normal albuminuria, ∆log e UACR and %TWL at 12 months were not correlated in either the medical therapy group or the LSG group (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519156).

**Relation of Change in Each Parameter with ∆log e UACR at 12 Months**

Table 3 shows the univariate analysis of the correlation between the change in each clinical or laboratory parameter and ∆log e UACR at 12 months, which included subjects with microalbuminuria and macroalbuminuria, regardless of the medical therapy or LSG. ΔLog e UACR was negatively correlated with %TWL. A significant negative correlation was also observed between LSG and Δlog e UACR. The presence of diabetes and the duration of diabetes were not associated with Δlog e UACR. The correlations between each parameter with Δlog e UACR at 12 months in the medical therapy group and the LSG group, respectively, were described in online supplementary Table 1.

Table 4 shows results of multiple regression analysis for the association between Δlog e UACR and changes in clinical variables identified as significant in the univariate analysis. Multiple regression analysis identified %TWL as the independent predictor of a decreased log e UACR (β coefficient = −0.460, p = 0.004). Whether LSG was performed or not was not selected as independent predictors.

**Usefulness of %TWL in Predicting the Decrease in the UACR at 12 Months**

We attempted to use %TWL for the prediction of the decrease in the UACR after medical therapy or LSG in patients with microalbuminuria or macroalbuminuria. ROC curves show the fraction of true-positive results (sensitivity) and false-positive results (1 –specificity) at a selected cutoff %TWL (Fig. 3). The cutoff %TWL that yielded the maximal sensitivity and specificity was 7.8%. At this cutoff value, the sensitivity was 60.8%, specificity was 71.8%, and the area under the curve was 0.658 (95% confidence interval: 0.545–0.770), and this ROC curve was statistically significant (p = 0.011). Over 95.9% of subjects in the LSG group had a %TWL ≥7.8% compared to 38.0% in the medical therapy group at 12 months.

**Discussion**

In this study, we compared LSG and conventional medical therapy regarding the outcome of albuminuria in Japanese severely obese subjects. The main results of this study were that continuation of medical therapy only could not prevent the increase in the UACR, while LSG prevented or even decreased the UACR and that %TWL contributed independently to the decrease in the UACR.
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Regardless of whether LSG was performed, percent TWL required is less likely to be achieved or sustained through medical therapy and compared to bariatric surgery interventions.

Several reports have shown that bariatric surgery improves albuminuria [8] or reduces the incidence of albuminuria compared with conventional medical therapy [11]. However, there have been no reports which evaluated the effects of bariatric surgery focusing on LSG in comparison with medical therapy in Japanese subjects with severe obesity.

LSG reduces excess weight by 69.7%, 1 year after the procedure [24], and 29.9% TWL can be achieved 2 years after operation [25]. Although weight loss at 2 years after LSG was not evaluated in this study, the degree of weight loss was generally consistent with previous reports. A remission rate of diabetes of approximately 86% following LSG has also been reported [26]. The rate of complete remission of diabetes was 77.4% in this study, which is slightly lower than the previous report but not by a large margin. This may be due to the difference in the definition of remission between trials.

It is important to note that while there are multiple reports that bariatric surgery decreases the UACR [8, 14, 27, 28], medical therapy did not decrease the UACR in this study despite significant weight loss. Since weight loss has been reported to be important in reducing the UACR [7], we examined the correlation between weight change and changes in the UACR in subjects with microalbuminuria and macroalbuminuria. We have previously reported that weight reduction therapy using a 4-week low-calorie diet improved proteinuria in obese subjects with diabetic nephropathy [29]. In the present analysis, 63.5% of the subjects in the medical therapy group and 80.3% of subjects in the LSG group had normal albuminuria. In the analysis of the remaining subjects with microalbuminuria and macroalbuminuria, weight loss correlated inversely with the change in log e UACR in both the medical therapy group and LSG group (Fig. 2). Although there was no significant correlation between the ∆log e UACR and %TWL at 36 months (data are not shown), this may have been due to the small sample size.

There was a higher percentage of subjects with microalbuminuria and macroalbuminuria in the medical therapy group, which was unexpected. The duration of diabetes might have influenced, but there was no significant difference between the 2 groups, and the exact cause of this result was not clear. On the other hand, it was suggested that patients with albuminuria may have inappropriately continued medical therapy and failed to transition to bariatric surgery.

Since the decrease in HbA1c and blood pressure are also considered important for the decrease in the UACR, we conducted a multiple regression analysis of factors contributing to the decrease in the UACR by including variables other than %TWL in the model. However, these factors were found to be unrelated. Initially, we thought that the decrease in HbA1c might contribute to the decrease in the UACR. Even the presence of diabetes did not contribute to the decrease in the UACR. There was also no correlation between duration of diabetes and decrease in the UACR. The presence of diabetic nephropathy is generally increase about 10 years after the diagnosis of diabetes [30], but in this study, the duration of diabetes was shorter than 10 years in both groups. Although we could not accurately diagnose diabetic nephropathy because we did not perform renal biopsy in the present subjects, it may be that the percentage of subjects who had diabetic nephropathy was not that high and the percentage of ORG was high. Therefore, the decrease in HbA1c

![Graph](image-url)
may not have contributed to the decrease in the UACR. Considering the possibility that LSG may have an influence on the decrease of the UACR, we included the presence or absence of LSG in the multiple regression analysis, but the presence or absence of LSG did not contribute independently to the decrease in the UACR.

Having found that weight loss contributed to the decrease in the UACR, we needed to determine the level of weight loss that contributed to decrease the UACR. The ROC curve using 7.8% weight loss as a cutoff was found to predict a decrease in the UACR. In the current study, the medical therapy group had a significant weight loss of 6.4% after 12 months of treatment and 6.2% after 36 months. These results suggest that while it is not impossible for medical therapy to achieve the degree of weight loss required to decrease the UACR, it may be difficult for many patients. Over 96.0% of subjects in the LSG group had a %TWL ≥7.8% compared to 38.0% in the medical therapy group. Therefore, although LSG does not independently contribute to the decrease in the UACR, bariatric surgery including LSG may be a preferable choice than conventional medical therapy to obtain adequate weight loss for the decrease in the UACR. Most importantly, continuation of medical therapy could not prevent the increase in the UACR over time in this study.

This study has several limitations. First, it was a retrospective study in a single institution, and some patients with no UACR data at 12 months were included. At 36 months analysis, the number of subjects with interrupted visits or no data was particularly high in the medical therapy group, which could affect the results of this study. Second, since the present study evaluated a period of only 36 months, a longer term study may yield different results from the current study. Third, renal biopsy was not performed, and we were unable to distinguish the effects of albuminuria due to diabetic nephropathy or hypertension from those due to obesity per se. We used the UACR instead of a 24-h urine collection which is the most reliable, gold standard method for reporting albuminuria. The majority of subjects in both groups had only residual levels of albuminuria, and the UACR is subjected to significant variations depending on a variety of factors. This could have an effect on our results. Furthermore, subjects taking angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors were also included so that the effects of these drugs on albuminuria cannot be ruled out. A prospective study with a larger sample and longer follow-up is needed to verify the present findings.

**Conclusions**

In Japanese subjects with severe obesity, albuminuria may increase over time if only conventional medical therapy is continued. For the improvement of albuminuria, weight loss may be more important than treatment with LSG. Nonetheless, medical therapy may not achieve sufficient weight loss needed to improve albuminuria, and bariatric surgery including LSG may be a preferred modality to obtain adequate weight loss.

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**Statement of Ethics**

The protocol of the study was prepared and implemented in accordance with the tenets of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Toho University Sakura Medical Center (approval date; Nov 28, 2018, approval No.; S18061). Although this was a retrospective study, we explained to individual patients for usage and release of study data and obtained written consent from each patient.

**Conflict of Interest Statement**

The authors declare that they have no conflicts of interest.

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**Author Contributions**

T.Y., A.S., and I.T. designed the original concept of this study. Y.W. wrote the initial draft of the manuscript. A.S. reviewed and edited the manuscript. All other authors contributed to data collection and interpretation and critically reviewed the manuscript. All the authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data Availability Statement**

Data described in the article will be made available upon reasonable request from the corresponding author.
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