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Preoperative Plasma Aldosterone Predicts Complete Remission of Type 2 Diabetes after Bariatric Surgery

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Keywords
Bariatric surgery · Type 2 diabetes · Plasma aldosterone concentration · Diabetes remission

Abstract

Introduction: Bariatric surgery (BS) has beneficial effects on body weight and type 2 diabetes. However, 44–52%, 20–40%, and 19–25% of patients with type 2 diabetes who undergo sleeve gastrectomy, sleeve gastrectomy with duodenal-jejunal bypass, and Roux-en-Y gastric bypass, respectively, show insufficient improvement 1 year after BS. It is thus important to predict the improvement in type 2 diabetes before BS. Many hormones are related to hyperglycemia. However, the relationship between hormones and improvement in type 2 diabetes after BS has not been studied. We aimed to evaluate the relationship between the improvement in type 2 diabetes and hormones in patients with obesity and type 2 diabetes who underwent BS. ***Methods:*** We retrospectively reviewed 79 patients with obesity and type 2 diabetes who underwent BS, with a follow-up period of 12 months. We analyzed the relationship between some clinical parameters and complete remission (CR) of type 2 diabetes after BS. Patients were divided into two groups (type 2 diabetes CR and non-CR). Multiple regression analysis was performed to determine the parameters associated with type 2 diabetes resolution after BS. ***Results:*** BS significantly improved body weight and glucose metabolism. Preoperative liver function, glycated hemoglobin (HbA1c), insulin secretion (homeostatic model assessment [HOMA]2-%B), renin activity, plasma aldosterone level, and duration of type 2 diabetes were significantly different between the CR and non-CR groups. Multiple regression analysis showed that preoperative HbA1c, HOMA2-%B, aldosterone concentration, and duration of type 2 diabetes were predictors of CR of type 2 diabetes after BS. Plasma aldosterone was the strongest predictor. ***Discussion/Conclusion:*** Preoperative plasma aldosterone levels were related to the CR of type 2 diabetes after BS. Measuring plasma aldosterone levels preoperatively is useful for predicting the CR of type 2 diabetes after BS.

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Introduction

Currently, bariatric surgery (BS) is the most effective weight loss therapy. It also has a positive effect on type 2 diabetes. BS significantly reduces glycated hemoglobin (HbA1c) levels compared to medical therapy alone (−2.1% vs. −0.3% at 5 years) [1]. Type 2 diabetes remission rates after BS at 2, 10, and 15 years are 72.3%, 38.1%, and 30.4%, respectively, which are significantly higher than those observed in controls [2]. Gastrointestinal therapeutic interventions, such as BS, for type 2 diabetes are classified as metabolic surgery [3, 4]; they improve glycemic control, as indicated by changes in HbA1c levels, which significantly decrease from 1 month after metabolic surgery and are maintained at <6.0% after 12 months [5]. Metabolic surgery reduces macrovascular and microvascular complications and mortality, compared to medical treatment in patients with type 2 diabetes [2, 6]. Thus, bariatric and metabolic surgery have excellent therapeutic effects on blood glucose control as well as diabetes complications in patients with type 2 diabetes.

Although bariatric and metabolic surgery are effective treatments for type 2 diabetes, 44–52%, 20–40%, and 19–25% of patients with type 2 diabetes who undergo sleeve gastrectomy (SG), SG with duodenal-jejunal bypass (DJB), and Roux-en-Y gastric bypass (RYGB), respectively, do not achieve remission of type 2 diabetes 1 year after bariatric and metabolic surgery [7–11]. Therefore, predicting type 2 diabetes remission after BS is important. Some clinical parameters have been reported as predictors of type 2 diabetes remission after BS [12–15]. We previously reported that preoperative serum insulin-like growth factor-1 (IGF-1) is a predictor of weight reduction after laparoscopic SG [16]. Our previous report indicated that preoperative hormones predict changes in clinical parameters after BS.

Some hormones are related to hyperglycemia. For instance, cortisol and growth hormones are important hyperglycemic factors [17, 18], and aldosterone is associated with insulin sensitivity and secretion [19]. These hormones may predict type 2 diabetes remission after BS. However, the relationship between type 2 diabetes and hormones in patients with obesity and type 2 diabetes who undergo BS has not been reported. Assessing the relationship between blood glucose and hormones in patients with obesity who undergo BS can aid the postoperative treatment of type 2 diabetes. Therefore, the aim of this study was to investigate the relationship between type 2 diabetes and hormones in patients with obesity and type 2 diabetes who underwent BS.

Materials and Methods

Study Design and Participants

We retrospectively reviewed clinical data obtained from November 2010 to January 2020 at the Toho University Sakura Medical Center (Sakura City, Chiba, Japan) to identify patients with type 2 diabetes who were treated for primary obesity (BMI ≥32 kg/m^2 at the first visit), who underwent BS, and were followed up for 12 months postoperatively. We excluded patients who could not be followed up for 12 months and those whose serum C-peptide level or visceral and subcutaneous fat area data at 12 months after BS were missing. The BMI criteria for BS in Japan are BMI ≥32 kg/m^2 with at least one obesity-related comorbidity such as type 2 diabetes, hypertension, or hyperlipidemia and BMI ≥35 kg/m^2, according to the guidelines of the Japanese Society for Treatment of Obesity. Of the patients with type 2 diabetes, 93 underwent BS during this period, and 6 dropped out within 12 months after BS. Serum C-peptide level and/or abdominal fat area were not measured for 8 patients at 12 months after BS. Overall, 14 patients were excluded from this study, and 84.9% (n = 79) of patients with type 2 diabetes who underwent BS at our hospital were included. The surgical procedures included SG (n = 62, 78.5%), gastric bypass (GB) (n = 3, 3.8%), and SG with DJB (n = 14, 17.7%). Patients with a BMI ≥35 kg/m^2 whose ABCD scores were below 5 or insulin users who could afford for a procedure that was more expensive (8,000 USD) than SG (800 USD) were eligible for SG with DJB [20]. Patients with a BMI ≥35 kg/m^2 or BMI ≥32 kg/m^2 with more than two obesity-related comorbidities and who could afford for a procedure that was more expensive (14,000–19,000 USD) than SG and SG with DJB were eligible for GB [20]. The other patients underwent SG because only SG is covered by the Japanese public medical insurance. We defined complete remission (CR) of type 2 diabetes as HbA1c <6.0% without using any diabetes medication 12 months after BS, according to previous reports [21, 22].

We compared the following parameters before BS and 12 months after BS: body weight (BW), BMI, aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), cholinesterase (ChE), blood urea nitrogen (BUN), serum creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol, fasting blood glucose (FBG), HbA1c, serum C-peptide, visceral fat area, subcutaneous fat area, steady state β-cell function homeostatic model assessment (HOMA)2 (HOMA2-%B), insulin sensitivity HOMA2 (HOMA2-%S), insulin resistance HOMA2 (HOMA2-IR), blood pressure (BP), and urinary albumin. The levels of serum growth hormone (GH), serum IGF-1, plasma adrenocorticotropic hormone (ACTH), plasma cortisol, plasma renin activity, plasma aldosterone concentration (PAC), serum thyroid-stimulating hormone (TSH), serum free tri-iodothyronine (FT3), and serum free thyroxine (FT4) were measured at baseline to discriminate secondary obesity from secondary metabolic disorders. The total weight loss percentage (%TWL) was estimated 12 months after BS. BW was measured, and blood samples were collected in the morning after a 12-h fast.

Measurements of Various Parameters

Within 1 h of blood collection, the serum and plasma were separated by centrifuging the specimen at 3000 rpm for 10 min. The serum and plasma were used to measure HbA1c, AST, ALT, GGT,

ChE, BUN, creatinine, eGFR, lipid, C-peptide, and hormone levels. Serum GH and plasma ACTH levels were measured by electrochemiluminescence immunoassay (ECLIA) using the ECLusys® reagent hGH or ECLusys® reagent ACTH assay kit (Roche Diagnostics, Basel, Switzerland). Serum IGF-1 levels were measured by immunoradiometric assay using the ECLusys® reagent IGF-1 assay kit (Roche). Plasma cortisol, serum TSH, serum FT3, and serum FT4 levels were measured by chemiluminescence immunoassay (CLIA) using the Cortisol Abbott, ARCHITECT TSH, FT3 Abbott, or FT4 Abbott (Abbott, Chicago, IL, USA). ECLIA was performed using cobas8000 (Roche Diagnostics, Basel, Switzerland). CLIA was performed using Architect i2000 SR (Abbott). Plasma renin activity was measured by enzyme immunoassay (EIA) using the YAMASA® Renin Activity Kit (YAMASA CORPORATION, Chiba, Japan). PAC was measured by radioimmunoassay (RIA) using the SPAC-S Aldosterone kit® (Fujirebio, Tokyo, Japan). EIA was performed using AP-X (Hitachi Chemical Company Ltd., Tokyo, Japan). RIA was performed using an ARC950 γ counter (Hitachi Ltd.). GH, IGF-1, ACTH, cortisol, aldosterone, and renin activity were measured at LSI Medience Corporation, Tokyo, Japan. TSH, FT3, and FT4 levels were measured at the Toho University Sakura Medical Center, Chiba, Japan. Visceral fat area was determined using computed tomography, which was performed at the umbilical level with the participant resting in the supine position. The subcutaneous fat area was calculated by subtracting the visceral fat area from the total fat area. Radiologists quantified the fat area using Ziostation2 software version 2.9.7.1 (Ziosoft, Inc., Tokyo, Japan).

Calculation of HOMA2-%B, HOMA2-%S, and HOMA2-IR

We used HOMA2, the updated HOMA model, to evaluate insulin secretion and resistance in this study. HOMA2 can account for variations in hepatic and peripheral glucose resistance [23]. HOMA2-%B, HOMA2-%S, and HOMA2-IR were determined using the HOMA2 Calculator (Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, United Kingdom). Glucose (mg/dL) and serum C-peptide (ng/mL) levels were used to calculate the HOMA2 score.

Statistical Analysis

The normality of data distribution was tested using the Shapiro-Wilk test. Continuous data are expressed as median and interquartile range (IQR), as many data were nonnormally distributed. Data were analyzed using the Wilcoxon signed-rank test (paired samples) or Wilcoxon rank-sum test (independent samples). Fisher's exact test was used to identify significant differences between the proportions and categorical variables. The χ^2 test was used to compare the three variables. Simple linear regression analysis was performed to analyze the correlation between CR of type 2 diabetes after BS and clinical parameters using Spearman's rank correlation coefficient, due to the nonparametric nature of all data. Multiple regression analysis was used to analyze the independent associations of variables with CR of type 2 diabetes. For correlation analyses, the presence or absence of CR in type 2 diabetes was coded as 1 and 0, respectively. Sensitivity and specificity with respect to CR of type 2 diabetes were analyzed using conventional receiver operating characteristic (ROC) curves. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using JMP software (version 14.3.0; SAS, Cary, NC, USA).

Results

Baseline Characteristics and Changes in Various Parameters 12 Months after BS

Table 1 shows the patients' baseline characteristics and changes in various parameters 12 months after BS. The median (IQR) age, BMI, and HbA1c were 44.0 (37.0–50.0) years, 43.1 (37.8–50.3) kg/m^2, and 6.8 (6.4–8.1)%, respectively. At 12 months after BS, the CR rate of type 2 diabetes was 64.6% ($n = 51$), and the median (IQR) %TWL was 27.4 (20.6–34.1%). The BW, BMI, and levels of visceral and subcutaneous fat significantly decreased after BS ($p < 0.0001$). TG, HDL-C, FBG, HbA1c, HOMA2-%S, HOMA2-IR, and urinary albumin levels also significantly improved. Serum C-peptide levels significantly decreased. Systolic and diastolic BP did not significantly change after BS.

Comparisons between Participants with and without CR of Type 2 Diabetes after BS

We divided all participants into two groups based on CR of type 2 diabetes after BS: CR and non-CR groups. Fifty-one (64.6%) and 28 (35.4%) patients were included in the CR and non-CR groups, respectively. The rates of surgical procedures, median age, and BMI did not differ between the two groups. AST, ALT, and GGT levels were significantly higher in the CR group than in the non-CR group. HbA1c was significantly lower and HOMA2-%B was significantly higher in the CR group than in the non-CR group (HbA1c: 6.6% [6.3%–7.0%] vs. 7.5% [6.7%–9.4%], $p = 0.0048$; HOMA2-%B: 102.5% [77.2%–121.9%] vs. 87.2% [60.1%–106.8%], $p = 0.0187$; Table 2). Renin activity and PAC were significantly lower in the CR group (renin activity: 1.9 [0.7–5.9] ng/mL/h vs. 3.5 [1.6–13.7] ng/mL/h, $p = 0.0219$; PAC: 123.0 [94.0–160.0] pg/mL vs. 175.0 [134.0–250.3] pg/mL, $p = 0.0002$; Table 2). The duration of type 2 diabetes was significantly shorter in the CR group than in the non-CR group (4.0 [2.0–10.0] years vs. 10.5 [4.5–15.0] years, $p = 0.0063$; Table 2). Other parameters were not significantly different between the groups.

Correlation between CR of Type 2 Diabetes (No, 0; Yes, 1) and Each Clinical Parameter at Baseline

Table 3 shows the correlation between CR of type 2 diabetes (no, 0; yes, 1) and each clinical parameter at baseline. AST, ALT, GGT, and HOMA2-%B showed a significant positive correlation with CR of type 2 diabetes after BS (AST: $\rho = 0.2711$, $p = 0.0157$; ALT: $\rho = 0.2873$, $p = 0.0102$; GGT: $\rho = 0.3041$, $p = 0.0064$; HOMA2-%B:

Table 1. Baseline characteristics and changes in various parameters 12 months after bariatric surgery

	Baseline	After 12 months	*p* value[a]
Subjects, *n*	79	–	–
Sex (male/female)	39 (49.4%)/40(50.6%)	–	–
Surgical procedure			
Sleeve gastrectomy/gastric bypass/sleeve gastrectomy with duodenal-jejunal bypass, *n* (%)	62 (78.5)/3 (3.8)/14 (17.7)	–	–
Complete remission of type 2 diabetes, *n* (%)	–	51 (64.6)	–
%TWL	–	27.4 (20.6–34.1)	–
Age, years	44.0 (37.0–50.0)	–	–
BW, kg	113.8 (99.0–143.6)	82.0 (71.3–101.7)	<0.0001
BMI, kg/m^2	43.1 (37.8–50.3)	30.5 (27.6–36.8)	<0.0001
AST, IU/L	29.0 (22.0–49.0)	18.0 (16.0–23.0)	<0.0001
ALT, IU/L	37.0 (22.0–66.0)	17.0 (13.0–23.0)	<0.0001
GGT, IU/L	36.0 (25.0–61.0)	20.0 (14.0–28.0)	<0.0001
ChE, IU/L	383.0 (338.0–438.0)	319.0 (269.0–359.0)	<0.0001
BUN, mg/dL	13.7 (11.0–17.3)	14.2 (11.2–18.4)	0.6298
Serum creatinine, mg/dL	0.67 (0.59–0.80)	0.65 (0.54–0.74)	0.0012
eGFR, mL/min/1.73 m^2	86.0 (75.0–96.0)	94.0 (76.0–105.0)	0.0050
Uric acid, mg/dL	7.0 (5.6–7.9)	6.0 (5.0–6.8)	<0.0001
TC, mg/dL	184.0 (160.0–198.0)	188.0 (163.0–208.0)	0.1110
TG, mg/dL	145.0 (115.0–191.0)	85.0 (61.0–130.0)	<0.0001
HDL-C, mg/dL	42.0 (36.0–47.0)	58.0 (48.0–71.0)	<0.0001
LDL-C, mg/dL	111.0 (95.0–135.0)	108.0 (92.0–126.0)	0.1636
FBG, mg/dL	120.0 (105.0–154.0)	103.0 (92.0–112.0)	<0.0001
HbA1c, %	6.8 (6.4–8.1)	5.8 (5.4–6.1)	<0.0001
Serum C-peptide, ng/mL	2.8 (2.2–3.5)	1.9 (1.4–2.7)	<0.0001
HOMA2-%B, %	96.7 (73.4–114.9)	91.2 (73.2–121.1)	0.4958
HOMA2-%S, %	41.9 (35.1–57.4)	65.4 (47.9–92.0)	<0.0001
HOMA2-IR	2.39 (1.74–2.85)	1.53 (1.09–2.09)	<0.0001
Systolic BP, mm Hg	132.0 (118.0–146.0)	130.0 (115.0–144.0)	0.5576
Diastolic BP, mm Hg	80.0 (70.0–86.0)	78.0 (70.0–89.0)	0.6194
Visceral fat area, cm^2	209.0 (159.0–250.1)	109.2 (70.1–149.4)	<0.0001
Subcutaneous fat area, cm^2	483.8 (370.5–700.0)	333.1 (231.8–445.3)	<0.0001
Urinary albumin, mg/g·Cr	16.7 (5.3–69.5)	7.6 (3.8–28.9)	0.0002
GH, ng/mL	0.16 (0.06–0.34)	–	–
IGF-1, ng/mL	113.0 (82.0–140.0)		–
ACTH, pg/mL	31.7 (20.9–43.4)	–	–
Cortisol, μg/mL	9.9 (7.7–14.0)	–	–
Renin activity, ng/mL/h	2.6 (0.9–8.1)	–	–
Aldosterone, pg/mL	139.0 (105.0–195.0)	–	–
TSH, μIU/mL	1.68 (1.02–2.47)	–	–
FT3, pg/mL	2.84 (2.30–3.14)	–	–
FT4, ng/dL	1.14 (1.04–1.30)	–	–
Duration of type 2 diabetes, years	7.0 (2.0–11.0)	–	–

Data are presented as median and interquartile range. TWL, total weight loss; BW, body weight; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; ChE, cholinesterase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HOMA, homeostatic model assessment; BP, blood pressure; GH, growth hormone; IGF, insulin-like growth factor; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FT3, free tri-iodothyronine; FT4, free thyroxine. [a] Wilcoxon signed-rank test.

ρ = 0.2669, p = 0.0174; Table 3). HbA1c level, renin activity, PAC, and duration of type 2 diabetes were significantly negatively correlated with the CR of type 2 diabetes after BS (HbA1c: ρ = −0.3202, p = 0.0040; renin activity: ρ = −0.2600, p = 0.0207; PAC: ρ = −0.4259, p < 0.0001; duration of type 2 diabetes: ρ = −0.3098, p = 0.0055; Table 3). The other variables did not show any significant correlations.

Table 2. Comparison of characteristics between participants with and without complete remission of type 2 diabetes (CR group and non-CR group)

	CR group	Non-CR group	*p* value
Subjects, *n*	51	28	
Sex (male/female)	25 (49)/26 (51)	14 (50)/14 (50)	1.0000[a]
Surgical procedure			
Sleeve gastrectomy/gastric bypass/sleeve gastrectomy with duodenal-jejunal bypass, *n* (%)	40 (78.4)/2 (3.9)/9 (17.6)	22 (78.6)/1 (3.6)/5 (17.9)	0.9968[b]
Age, years	44.0 (36.0–49.0)	44.0 (39.5–50.0)	0.7388[c]
BW, kg	113.8 (99.7–148.4)	115.3 (95.8–134.6)	0.5835[c]
BMI, kg/m^2	43.7 (37.8–52.1)	42.0 (37.8–48.5)	0.4763[c]
AST, IU/L	32.0 (24.0–57.0)	25.5 (19.0–34.8)	0.0169[c]
ALT, IU/L	41.0 (24.0–77.0)	27.5 (17.8–43.5)	0.0113[c]
GGT, IU/L	49.0 (28.0–73.0)	30.5 (19.5–43.0)	0.0073[c]
ChE, IU/L	384.0 (348.0–438.0)	366.0 (328.0–438.8)	0.5352[c]
BUN, mg/dL	13.4 (10.9–15.9)	15.1 (12.1–21.3)	0.0851[c]
Serum creatinine, mg/dL	0.65 (0.59–0.80)	0.69 (0.59–0.83)	0.4729[c]
eGFR, mL/min/1.73 m^2	87.0 (79.0–100.0)	84.5 (65.3–89.8)	0.1052[c]
UA, mg/dL	7.1 (5.4–7.9)	6.4 (5.6–7.8)	0.9469[c]
TC, mg/dL	185.0 (166.0–200.0)	173.0 (143.3–196.8)	0.0968[c]
TG, mg/dL	150.0 (113.0–198.0)	140.5 (119.0–181.3)	0.9143[c]
HDL-C, mg/dL	42.0 (37.0–47.0)	40.5 (32.0–48.5)	0.4266[c]
LDL-C, mg/dL	114.0 (98.0–138.0)	106.5 (83.8–128.5)	0.0823[c]
FBG, mg/dL	121.0 (105.0–144.0)	118.5 (105.0–181.8)	0.4667[c]
HbA1c, %	6.6 (6.3–7.0)	7.5 (6.7–9.4)	0.0048[c]
Serum C-peptide, ng/mL	2.8 (2.3–3.7)	2.5 (1.8–3.3)	0.2127[c]
HOMA2-%B, %	102.5 (77.2–121.9)	87.2 (60.1–106.8)	0.0187[c]
HOMA2-%S, %	42.8 (34.6–56.5)	40.7 (35.3–71.0)	0.7121[c]
HOMA2-IR	2.34 (1.77–2.89)	2.5 (1.4–2.8)	0.7045[c]
Systolic BP, mm Hg	133.0 (118.0–148.0)	125.5 (118.0–140.3)	0.1929[c]
Diastolic BP, mm Hg	80.0 (70.0–88.0)	79.0 (70.0–86.0)	0.6153[c]
Visceral fat area, cm^2	211.6 (162.4–262.5)	186.6 (146.8–233.3)	0.2531[c]
Subcutaneous fat area, cm^2	509.3 (362.6–707.0)	483.6 (391.6–628.1)	0.8738[c]
Urinary albumin, mg/g·Cr	14.3 (5.0–34.1)	23.8 (5.7–295.6)	0.2637[c]
GH, ng/mL	0.15 (0.05–0.32)	0.2 (0.07–0.36)	0.5351[c]
IGF-1, ng/mL	117.0 (85.0–143.0)	98.5 (77.8–128.3)	0.2074[c]
ACTH, pg/mL	31.7 (21.5–40.8)	32.8 (20.0–46.5)	0.7859[c]
Cortisol, μg/mL	9.7 (7.7–12.5)	11.6 (7.7–15.3)	0.1229[c]
Renin activity, ng/mL/h	1.9 (0.7–5.9)	3.5 (1.6–13.7)	0.0219[c]
Aldosterone, pg/mL	123.0 (94.0–160.0)	175.0 (134.0–250.3)	0.0002[c]
TSH, μIU/mL	1.68 (0.94–2.56)	1.68 (1.06–2.38)	0.8940[c]
FT3, pg/mL	2.92 (2.33–32.0)	2.70 (2.28–3.09)	0.1810[c]
FT4, ng/dL	1.13 (1.02–1.28)	1.21 (1.09–1.35)	0.0814[c]
Duration of type 2 diabetes, years	4.0 (2.0–10.0)	10.5 (4.5–15.0)	0.0063[c]

Data are presented as median and interquartile range. BW, body weight; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; ChE, cholinesterase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HOMA, homeostatic model assessment; BP, blood pressure; GH, growth hormone; IGF, insulin-like growth factor; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FT3, free tri-iodothyronine; FT4, free thyroxine. [a] Fisher's exact test. [b] χ^2 test. [c] Wilcoxon signed-rank test.

Association between CR of Type 2 Diabetes and Dependent Variables

Baseline values of AST, ALT, GGT, HbA1c, HOMA2-%B, renin activity, PAC, and duration of type 2 diabetes were significantly correlated with the CR of type 2 diabetes (Table 3). We excluded AST and ALT from the models because of their correlation with GGT levels. Although the duration of type 2 diabetes was intercorrelated with HbA1c and HOMA2-%B, it was included in the analysis because it significantly affects both islet func-

Table 3. Correlation between complete remission of type 2 diabetes (no, 0; yes, 1) and each preoperative clinical parameter

	Complete remission of type 2 diabetes (no, 0; yes, 1)	
	ρ	*p* value
Sex (male, 0; female, 1)	0.0094	0.9346
Surgical procedure (sleeve, 0; bypass, 1)	0.0016	0.9886
Age (years)	−0.0383	0.7373
BW (kg)	0.0627	0.5832
BMI (kg/m^2)	0.0812	0.4767
AST (IU/L)	0.2711	0.0157
ALT (IU/L)	0.2873	0.0102
GGT (IU/L)	0.3041	0.0064
ChE (IU/L)	0.0708	0.5353
BUN (mg/mL)	−0.1956	0.0841
Serum creatinine (mg/mL)	−0.0818	0.4733
eGFR (mL/min/1.73 m^2)	0.1840	0.1045
UA (mg/dL)	0.0081	0.9433
TC (mg/dL)	0.1886	0.0960
TG (mg/dL)	0.0128	0.9111
HDL-C (mg/dL)	0.0906	0.4272
LDL-C (mg/dL)	0.1973	0.0813
FBG (mg/dL)	−0.0830	0.4671
HbA1c (%)	−0.3202	0.0040
Serum C-peptide (ng/mL)	0.1417	0.2130
HOMA2-%B (%)	0.2669	0.0174
HOMA2-%S (%)	−0.0424	0.7109
HOMA2-IR	0.0435	0.7033
Systolic BP (mm Hg)	0.1480	0.1930
Diastolic BP (mm Hg)	0.0575	0.6148
Visceral fat area (cm^2)	0.1300	0.2536
Subcutaneous fat area (cm^2)	0.0186	0.8710
Urinary albumin (mg/g·Cr)	−0.1334	0.2641
GH (ng/mL)	−0.0708	0.5352
IGF-1 (ng/mL)	0.1433	0.2076
ACTH (pg/mL)	−0.0313	0.7840
Cortisol (μg/mL)	−0.1753	0.1224
Renin activity (ng/mL/h)	−0.2600	0.0207
Aldosterone (pg/mL)	−0.4259	<0.0001
TSH (μIU/mL)	−0.0157	0.8910
FT3 (pg/mL)	0.1520	0.1810
FT4 (ng/dL)	−0.1979	0.0804
Duration of type 2 diabetes (years)	−0.3098	0.0055

Bypass refers to gastric bypass and sleeve gastrectomy with duodenal-jejunal bypass. BW, body weight; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; ChE, cholinesterase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HOMA, homeostatic model assessment; BP, blood pressure; GH, growth hormone; IGF, insulin-like growth factor; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FT3, free tri-iodothyronine; FT4, free thyroxine.

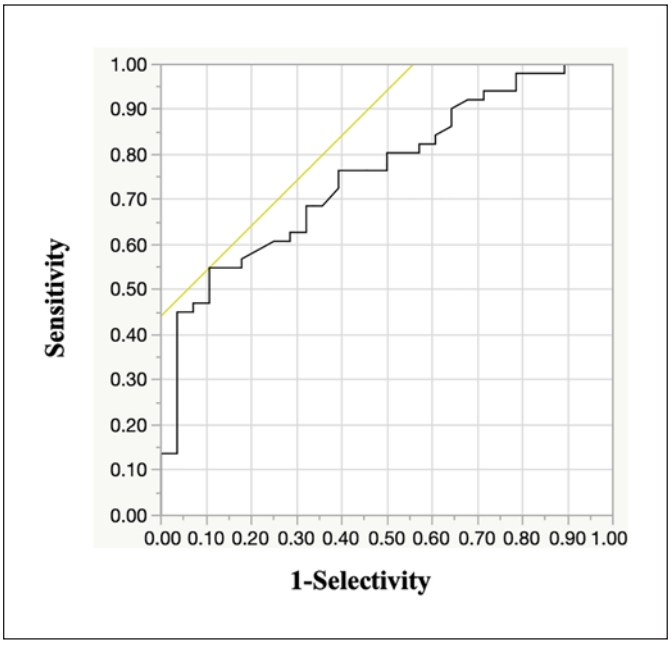

Fig. 1. Usefulness of plasma aldosterone level in the prediction of complete remission of type 2 diabetes (no or yes) 1 year after bariatric surgery. The curve represents the ROC curve for the prediction of complete remission of type 2 diabetes. The AUC of aldosterone exhibited the highest value (AUC; 0.7570). The sensitivity and specificity were the highest when the cutoff value for plasma aldosterone was 124.0 pg/mL (sensitivity, 54.9%; specificity, 55.8%). The 95% CI was 0.6348–0.8481, $p = 0.0017$. AUC, area under the ROC curve; ROC, receiver operating characteristic; CI, confidence interval.

tion and insulin sensitivity, thus influencing type 2 diabetes remission. Therefore, we made two multiple regression models because of the influences of multicollinearity: one included sex, age, GGT, HbA1c, HOMA2-%B, renin activity, and PAC (model 1), and the other included sex, age, GGT, renin activity, PAC, and duration of type 2 diabetes (model 2). Table 4 summarizes the results of the multiple regression analysis performed to identify the association between the CR of type 2 diabetes and other clinical variables. Model 1 showed that preoperative HbA1c, HOMA2-%B, and PAC were independent predictors of CR in type 2 diabetes after BS (HbA1c: standardized β = 0.2587, $p = 0.0266$; HOMA2-%B: standardized β = 0.1973, $p = 0.0438$; PAC: standardized β = −0.3712, $p = 0.0004$). Model 2 showed that PAC and duration of type 2 diabetes were independent predictors of CR in type 2 diabetes after BS (PAC: standardized β = −0.3295, $p = 0.0029$; duration of type 2 diabetes: standardized β = −0.2461, $p = 0.0321$). PAC was the major independent predictor of CR in type 2 diabetes after BS.

Table 4. Correlation of complete remission of type 2 diabetes (no, 0; yes, 1) with other preoperative variables analyzed by multiple regression models

	Model 1 standardized β	SE	*p* value	Model 2 standardized β	SE	*p* value
Sex (male, 0; female, 1)	0.1149	0.0977	0.2644	0.0662	0.1038	0.5436
Age (years)	−0.0164	0.0056	0.8711	0.0153	0.0063	0.8939
GGT (IU/L)	0.1634	0.0010	0.1000	0.1161	0.0011	0.2706
HbA1c (%)	−0.2587	0.0334	0.0266	–	–	–
HOMA2-%B (%)	0.1973	0.0013	0.0438	–	–	–
Renin activity (ng/mL/h)	−0.1778	0.0051	0.0752	−0.1288	0.0054	0.2206
Aldosterone (pg/mL)	−0.3712	0.0005	0.0004	−0.3295	0.0005	0.0029
Duration of type 2 diabetes (years)	–	–	–	−0.2461	0.0078	0.0321

Model 1: $r^2 = 0.3443$, $p < 0.0001$; model 2: $r^2 = 0.2424$, $p = 0.0022$. SE, standard error; GGT, γ-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model assessment.

Other variables at baseline were not found to be independent predictors of CR (Table 4).

Usefulness of Baseline PAC in the Prediction of CR of Type 2 Diabetes (No, 0; Yes, 1) after BS

We attempted to use baseline PAC for the prediction of CR in type 2 diabetes (no or yes) after BS. The ROC curves show the fraction of true-positive results (sensitivity) and false-positive results at the cutoff PAC (Fig. 1). The cutoff value of PAC that yielded the maximal sensitivity and specificity was 124.0 pg/mL. At this cutoff value, the sensitivity was 54.9%, specificity was 55.8%, and area under the ROC curve was 0.7570. The ROC curve was significant ($p = 0.0017$) (Fig. 1).

Comparisons between Participants with Low (<124.0 pg/mL) and High (≥124.0 pg/mL) PAC

We estimated the cutoff value of PAC for predicting the CR of type 2 diabetes after BS from the ROC curve (Fig. 1). We divided all participants into two groups: low aldosterone (<124.0 pg/mL) and high aldosterone (≥124.0 pg/mL) groups. Twenty-nine and 50 patients were included in the low and high PAC groups, respectively. PAC was significantly higher, and the rate of postoperative diabetes remission was significantly lower in the high aldosterone group than in the low aldosterone group (Table 5). Other parameters were not significantly different between the groups.

Comparisons between SG Group and GB or SG with DJB Group

Given the differences in the effects of SG and bypass procedures on glucose metabolism, we compared the SG group ($n = 62$) and GB or SG with DJB group (bypass group) ($n = 17$). Preoperative age, BW, BMI, PAC, and duration of type 2 diabetes were not different between the two groups. However, FBG and HbA1c were significantly higher in the bypass group than in the SG group (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000521855). There was a significant correlation between preoperative PAC and CR of type 2 diabetes (no, 0; yes, 1) in both groups (online suppl. Table 2). The correlation coefficient was −0.3796 ($p = 0.0023$) in the SG group and −0.6281 ($p = 0.0069$) in the bypass group (online suppl. Table 2).

Discussion/Conclusion

In the present study, BS led to significant reductions in BW, BMI, FBG, and HbA1c levels. BS also significantly improved HOMA2-%S and HOMA2-IR. The participants were divided into two groups: with CR and non-CR of type 2 diabetes. The PAC was significantly higher in participants with non-CR of type 2 diabetes. The multiple regression model showed that preoperative HbA1c level, HOMA2-%B, PAC, and duration of type 2 diabetes were independent predictors of CR in type 2 diabetes after BS. Preoperative PAC was the major independent predictor of CR in patients with type 2 diabetes after BS. The ROC curve showed that the cutoff value of PAC for CR of type 2 diabetes was 124.0 pg/mL. The rate of CR of type 2 diabetes was significantly low in participants with ≥124.0 pg/mL aldosterone.

Our study demonstrated that preoperative PAC was related to the CR of type 2 diabetes after BS. High aldosterone

Table 5. Comparison of characteristics between participants with lower and higher plasma aldosterone concentration

	Aldosterone <124.0 pg/mL	Aldosterone ≥124.0 pg/mL	*p* value
Preoperative			
Subjects, *n*	29	50	
Sex (male/female)	17 (58.6)/12 (41.4)	22 (44.0)/28 (56.0)	0.2481[a]
Surgical procedure			
Sleeve gastrectomy/gastric bypass/sleeve gastrectomy with duodenal-jejunal bypass, *n* (%)	23 (79.3)/1 (3.4)/5 (17.2)	39 (78.0)/2 (4.0%)/9 (18.0)	0.9877[b]
Age, years	43.0 (38.5–49.5)	44.0 (36.8–50.0)	0.9919[c]
BW, kg	118.0 (104.3–148.9)	112.4 (95.6–140.9)	0.3140[c]
BMI, kg/m^2	43.7 (39.2–52.1)	40.9 (36.8–50.2)	0.2632[c]
AST, IU/L	30.0 (24.0–50.5)	27.5 (21.8–50.3)	0.6580[c]
ALT, IU/L	39.0 (22.0–67.5)	33.0 (22.0–66.5)	0.6544[c]
GGT, IU/L	35.0 (24.5–67.0)	43.0 (25.5–61.0)	0.9069[c]
ChE, IU/L	383.0 (316.5–436.5)	381.5 (343.0–441.8)	0.4988[c]
BUN, mg/dL	13.0 (11.1–.2)	13.8 (10.9–17.4)	0.8388[c]
Serum creatinine, mg/dL	0.65 (0.58–0.81)	0.68 (0.59–0.81)	0.8587[c]
eGFR, mL/min/1.73 m^2	86.0 (79.5–95.5)	85.5 (74.6–98.8)	0.7679[c]
FBG, mg/dL	121.0 (101.5–149.0)	117.5 (105.8–155.0)	0.6181[c]
HbA1c, %	6.6 (6.4–8.5)	6.9 (6.3–8.1)	0.5788[c]
HOMA 2-%B, %	92.0 (73.3–121.7)	97.7 (73.3–113.4)	0.9757[c]
HOMA 2-%S, %	41.3 (35.4–65.5)	42.4 (34.6–57.7)	0.8627[c]
HOMA 2-IR	2.42 (1.56–2.83)	2.37 (1.73–2.89)	0.8627[c]
Systolic BP, mm Hg	139.0 (116.0–154.5)	130.0 (118.0–138.3)	0.1220[c]
Diastolic BP, mm Hg	80.0 (72.5–87.0)	78.5 (69.8–86.0)	0.5687[c]
Urinary albumin, mg/g·Cr	14.9 (5.5–94.3)	16.7 (5.2–53.6)	0.8237[c]
Renin activity, ng/mL/h	1.2 (0.6–9.9)	2.9 (1.6–7.6)	0.1443[c]
Aldosterone, pg/mL	95.0 (82.0–107.5)	175.5 (142.5–210.0)	<0.0001[c]
Duration of type 2 diabetes, years	5.0 (2.5–10.5)	7.0 (2.0–11.3)	0.8743[c]
Postoperative			
Remission of type 2 diabetes, *n* (%)	26 (89.7)	25 (50.0)	0.0005[a]
%TWL	29.1 (22.6–35.6)	27.4 (18.9–32.7)	0.2000[c]
ΔBW, kg	−35.7 (−45.6 to 25.5)	−32.7 (−39.4 to 20.3)	0.1258[c]
ΔBMI, kg/m^2	−12.0 (−16.3 to 10.1)	−11.7 (−14.5 to 8.1)	0.1284[c]
ΔFBG, mg/dL	−20.0 (−51.5 to 0.5)	−15.5 (−40.3 to 4.5)	0.6729[c]
ΔHbA1c, %	−1.2 (−2.3 to 0.8)	−0.9 (−1.9 to 0.4)	0.0940[c]
ΔHOMA2-%B, %	1.7 (−25.7 to 31.6)	−1.9 (−20.8 to 26.1)	0.7797[c]
ΔHOMA2-%S, %	28.1 (7.1–56.35)	20.8 (1.1–34.8)	0.2611[c]
ΔHOMA2-IR	−0.8 (−1.6 to 0.2)	−0.8 (−1.2 to 0.0)	0.4365[c]

Data are presented as median and interquartile range. Δ represents the difference between the values at baseline and after 12 months. BW, body weight; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; GGT, γ-glutamyl transpeptidase; ChE, cholinesterase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model assessment; BP, blood pressure; TWL, total weight loss. [a] Fisher's exact test. [b] χ^2 test. [c] Wilcoxon signed-rank test.

levels are associated with insulin resistance and incident type 2 diabetes. The prevalence of type 2 diabetes is high in patients with primary aldosteronism [24, 25]. Some mechanisms of the association between aldosteronism and diabetes, especially insulin resistance, have been proposed. A decrease in aldosterone is related to a decrease in HOMA-IR and an increase in adiponectin levels [26]. Aldosterone decreases adiponectin and diminishes the effect of rosiglitazone on increasing adiponectin levels in 3T3-L1 adipocytes [27]. Aldosterone decreases insulin-induced glucose uptake by decreasing the phosphorylation of mitogen-activated protein kinase and Akt and by degradation of insulin receptor substrate (IRS) 1 and IRS 2 in cultured adipocytes [28, 29]. Aldosterone suppresses glucose transporter type 4 translocation in adipocytes and skeletal muscle [30]. Inhibition of the aldosterone effect via mineralocorticoid

receptor inhibitors improves glucose uptake in skeletal muscle [31]. Thus, aldosterone is associated with insulin resistance in adipocytes and skeletal muscles. However, our study did not show a relationship between preoperative PAC and insulin resistance preoperatively and postoperatively. The mechanisms by which PAC relates to the CR of type 2 diabetes after BS are still unknown.

The mechanisms by which PAC relate to CR of type 2 diabetes were not clarified in the study. However, our results suggest that aldosterone blockade improves blood glucose in clinical situations. Eplerenone, a mineralocorticoid receptor antagonist, attenuates obesity-related insulin resistance, partly by reducing the production of reactive oxygen species, inflammatory processes, and induction of cytokines in obese mice [32]. Eplerenone also diminishes insulin resistance, partly by reducing the action of the renin-angiotensin-aldosterone system, inflammatory progression, and cytokine induction in mice [33]. Although aldosterone blockade improves insulin resistance in animal models, a meta-analysis showed that spironolactone has significant or nonsignificant negative effects. Eplerenone and canrenone have neutral effects on glycemia [34]. The relationship between blood glucose and esaxerenone, a newly developed mineralocorticoid blocker, has not been studied sufficiently. No patient in this study used mineralocorticoid blockers. Further studies are needed to clarify the effect of aldosterone blockade on type 2 diabetes.

Bypass procedures are associated with higher rates of type 2 diabetes remission than SG [7–11]. Some mechanisms that explain why diabetes improves after BS have been put forth; an increase in GLP-1 secretion after BS is one of such mechanisms [35]. GLP-1 secretion is increased after bypass procedures and SG, and the effect is stronger in bypass procedures than in SG [36]. Both GLP-1 and insulin secretion at 30 min after a meal test are significantly increased after RYGB [37]; GB is associated with a greater increase in insulin secretion in the oral glucose tolerance test than SG, which may explain type 2 diabetes remission after BS [38]. Furthermore, GLP-1 suppresses PAC [39]; aldosterone is known to reduce insulin secretion [40]. PACs decrease after GB [41]. Therefore, suppression of PAC by increasing GLP-1 secretion may be a mechanism of increase of insulin secretion after BS. PACs may reduce more with bypass procedures than SG because bypass procedures increase GLP-1 secretion than SG [36]. The correlation coefficient between type 2 diabetes remission after surgery and preoperative PAC was 1.6-fold higher in bypass procedures than in SG in this study. The relationship between GLP-1, aldosterone, and insulin secretion may be one of the mechanisms that explain the higher remission rates of type 2 diabetes after BS in bypass procedures than in SG. However further study is needed to clarify this mechanism.

Our study showed that preoperative insulin secretion is related to the CR of type 2 diabetes after BS. Other studies and our previous study have also shown that higher preoperative serum C-peptide levels or better β-cell function are associated with type 2 diabetes remission after BS [12, 15, 42–44]. Higher insulin secretion represents the preservation of β-cell function. Although BS improves type 2 diabetes, the recovery of β-cell function is limited after RYGB [45]. Thus, sufficient preoperative insulin secretion is necessary for the CR of type 2 diabetes after BS.

This study has a few limitations. First, PAC was not measured in any patient after BS. If PAC was measured in all patients after BS, we would have been able to determine whether PAC decreased after BS. Further prospective research is needed to clarify changes in plasma renin activity and PAC after BS. Second, there were three types of surgeries in this study; the rates of CR for type 2 diabetes were 64.5% (40/62), 66.7% (2/3), and 64.3% (9/14) in patients who underwent SG, GB, and SG with DJB, respectively. Although there was no significant difference in the CR rates between the surgery types, the patients with type 2 diabetes in this study who underwent bypass procedures had more severe disease than those who underwent SG. However, the rates of types of surgical procedures were not different between the low and high PAC groups. Finally, as this was a single-center retrospective study, the sample size was small. Future studies with a large number of patients with obesity, a control group, and use of multiple medical centers in Japan and possibly other Asian countries are needed. Despite these limitations, we were able to show that preoperative PAC was a predictor of CR in type 2 diabetes after BS.

In conclusion, preoperative PAC is related to the CR of type 2 diabetes after BS. Measuring PAC preoperatively is useful for predicting the CR of type 2 diabetes after BS. However, the mechanisms by which preoperative PAC is related to the CR of type 2 diabetes and changes in plasma renin activity and PAC after BS are still unknown. Further studies are needed to clarify these.

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Statement of Ethics

The protocol of the study was prepared in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Toho University Sakura Medical Center (approval date: November 28, 2018; Approval No. S18061). Our institute waived the need to obtain written informed consent due to the retrospective study design.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.O. contributed to the research concept and design, collection and/or assembly of data, data analysis, and writing of the article. K.A. contributed to the collection and assembly of data. T.Y. contributed to the collection and assembly of data. H.O. contributed to the collection and assembly of data. S.Y. contributed to the collection and assembly of data. S.N. contributed to the collection and assembly of data. S.T. contributed to the collection and assembly of data. Y.W. contributed to the collection and assembly of data. T.N. contributed to the collection and assembly of data. T.O. contributed to the collection and assembly of data. D.N. contributed to data interpretation. A.S. contributed to the collection and/or assembly of the data and critical revision of the manuscript. I.T. contributed to data interpretation and critical revision of the manuscript. All authors approved the version to be published.

Data Availability Statement

Data generated and/or analyzed during this research are available from the corresponding author on reasonable request.

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