

Bariatric Surgery can Reduce Albuminuria in Patients with Severe Obesity and Normal Kidney Function by Reducing Systemic Inflammation

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Abstract

Background Obesity causes renal problems including albuminuria. Bariatric surgery (BS) improves albuminuria. We investigated whether albuminuria is reduced by weight loss per se or by improved systemic inflammation induced by weight loss after BS.

Methods Patients older than 18 years who received BS in Soonchunhyang University Hospital from 01 January 2011 to 31 December 2011 were included. Other inclusion criteria included body mass index (BMI) ≥ 30 kg/m², creatinine level ≤ 1.0 mg/dL, and no overt proteinuria (trace amount or undetectable by dipstick). The patients were followed at 1 and 6 months after BS.

Results Forty-three patients were analyzed. Three patients were men, 10 patients had diabetes, and 12 patients had hypertension. All patients had normal renal function (creatinine ≤ 1.0 mg/dL), and estimated glomerular filtration rate was 115.7 ± 16.5 mL/min/1.73 m². There were significant reductions in body weight, BMI, high-sensitivity C-reactive protein (hs-CRP), and urine albumin-to-creatinine ratio (ACR). There were positive correlations between delta hs-CRP and delta body weight ($r = 0.349$, $p = 0.043$) or delta body mass index (BMI, $r = 0.362$, $p = 0.035$); between hs-CRP and body weight ($r = 0.374$, $p = 0.001$), BMI ($r = 0.431$, $p < 0.001$). Multivariate analysis using a linear mixed model demonstrated

that hs-CRP ($\beta = 0.5364$, $p = 0.026$) was an independent risk factor affecting ACR.

Conclusions Our study suggests that BS can reduce albuminuria in patients with severe obesity and normal kidney function by reducing systemic inflammation.

Keywords Bariatric surgery · Albuminuria · Proteinuria · Systemic inflammation

Introduction

Obesity is a condition associated with metabolic abnormalities, including systemic inflammation, insulin resistance, and impaired glucose and lipid metabolism [1]. These abnormalities result in complications, such as coronary artery disease, stroke, and type 2 diabetes mellitus, and are associated with increased mortality [2, 3]. Lifestyle modification is a traditional treatment of obesity [4] but may not be adequate enough to produce a promising effect. Laparoscopic bariatric surgery (BS) lowers body weight and body mass index (BMI) and improves systemic inflammation, insulin resistance, glucose and lipid metabolism, and blood pressure [5].

Obesity is associated with renal disease, including proteinuria, chronic kidney disease (CKD), and progression to end-stage renal disease [6, 7]. A study of 95 patients with severe obesity reported 77% of the patients had glomerular lesions associated with obesity [8]. Albuminuria is an independent risk of cardiovascular disease [9], and the reduction of albuminuria decreases the cardiovascular risk [10, 11]. Weight loss improves the glomerular filtration rate (GFR), reduces proteinuria, resolves pathologic lesions, and decreases cardiovascular risk [12–16]. The mechanism of obesity-related kidney damage has been described [7, 17]. Weight loss, with or without BS, improves renal function and reduces proteinuria via

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improved blood pressure and glucose metabolism, and reduced systemic inflammation associated with weight loss [18]. However, it is unclear whether BS-mediated reduction in albuminuria is due to weight loss per se or by improved systemic inflammation induced by weight loss.

The present prospective study explored whether weight loss directly reduces albuminuria, or indirectly reduces albuminuria via improvement of systemic inflammation induced by weight loss.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (IRB No. SCHCA_IRB_2011-78). All patients provided their written informed consent.

Subjects

This prospective cohort study included patients older than 18 years who received BS at Soonchunhyang University Hospital Obesity Surgery Center from 01 January 2011 to 31 December 2011. Other inclusion criteria were BMI ≥ 30 kg/m², creatinine level ≤ 1.0 mg/dL, and absence of overt proteinuria indicated by trace or undetectable dipstick test result. The patients were followed up by a physician 1 and 6 months after discharge.

Data Collection

Clinical parameters collected perioperatively included age, sex, status of hypertension and/or diabetes, blood pressure, weight, height, BMI, and type of surgical technique. The percentage of excess weight loss (%EWL) was calculated as weight reduction during observation period/(actual body weight – ideal body weight), which represented the ideal body weight equivalent to a BMI of 23 kg/m², which is the upper limit of normality in Asians according to the World Health Organization definition [19].

White blood cell (WBC) count, hemoglobin (Hb), platelet count, serum albumin, fasting glucose, aspartate transaminase (AST), alanine aminotransferase (ALT), total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol, triglyceride, blood urea nitrogen, serum creatinine, uric acid, high-sensitivity C-reactive protein (hs-CRP), and urine albumin-creatinine ratio (ACR) were determined. GFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20]. Glycated hemoglobin (HbA1c) was measured only in patients with diabetes.

Known novel biomarkers including serum monocyte chemoattractant protein-1 (Quantikine® ELISA, Human CCL2/MCP-1 Immunoassay kit; R&D Systems, Minneapolis, MN, USA), human cartilage glycoprotein-39 (Quantikine® ELISA, Human Chitinase 3-like 1 Immunoassay kit; R&D Systems), methylglyoxal (OxiSelect™ Methylglyoxal kit; Cell Biolabs, San Diego, CA, USA), N ϵ -(carboxymethyl) lysine (OxiSelect™ N ϵ -(carboxymethyl) lysine ELISA kit; Cell Biolabs), high molecular weight adiponectin (Quantikine® ELISA, Human HMW Adiponectin/Acrp30 Immunoassay kit; R&D Systems), leptin (Quantikine®, Human Leptin Immunoassay kit; R&D Systems), and urine leptin-to-creatinine ratio were measured to evaluate whether these biomarkers could predict the degree of reduction in BMI or body weight after BS.

Statistical Analysis

Continuous data are presented as the mean \pm standard error or the median (interquartile range), and categorical data are presented as frequencies (percentages or number of samples). The difference of continuous data between preoperative and postoperative values was evaluated using paired *t* test or Wilcoxon signed-rank test, as appropriate. Continuous data that did not follow the normal distribution were log-transformed to analyze. Delta values were obtained by subtracting value measured 6 months after BS from the value at baseline.

Pearson's correlation analysis or Spearman's rank correlation was performed to evaluate the correlation coefficient, and partial correlation coefficient analysis was performed when the controls on confounding factors are needed. Univariate and multivariate analysis using linear mixed model was used to evaluate independent risk factors that affect the degree of proteinuria, with the values confirmed $p < 0.50$ in univariate analysis or thought clinically relevant. SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

Forty-seven patients were included in the study. Four were excluded due to loss of follow-up. Thus, 43 patients were finally analyzed. The median age was 32 years (26–45 years), and the follow-up duration was 6 months. Three patients were male, 10 patients had diabetes, and 12 had hypertension. Twenty-six patients had received laparoscopic Roux-en-Y gastric bypass, and 17 patients had received laparoscopic sleeve gastrectomy (Table 1). All patients had normal creatinine levels (≤ 1.0 mg/dL) without overt proteinuria (dipstick \leq trace), and estimated GFR (eGFR) estimated by the CKD-EPI equation was 115.7 ± 16.5 mL/min/1.73 m² (Table 2). ACR

Table 1 Baseline characteristics of the patients (*n* = 43)

Parameters	Characteristics
Age	32 (26–45)
Sex	Male 3 Female 40
Hypertension	12 (27.3%)
Diabetes	10 (22.7%)
Surgical technique	LRYGB 26 SG 17

LRYGB laparoscopic Roux-en Y gastric bypass, SG laparoscopic sleeve gastrectomy

was in the normal range (< 30 mg/g) for 27 patients, 13 patients had microalbuminuria (30–300 mg/g), and three patients had macroalbuminuria (> 300 mg/g). After BS, only four patients continued to display microalbuminuria and none displayed macroalbuminuria.

BS produced significant decrease in body weight, BMI, WBC, Hb, platelet, AST, ALT, total cholesterol, triglyceride, uric acid, hs-CRP, creatinine, ACR, eGFR, and HbA1c (measured only in diabetic patients, *n* = 10) (Table 2). The average

%total weight loss (%TWL) was 20.4 ± 7.7%. The median %EWL was 49.8% (39.4–69.9%). There were positive correlations between delta hs-CRP and delta body weight (*r* = 0.349, *p* = 0.043, Fig. 1a) and delta BMI (*r* = 0.362, *p* = 0.035, Fig. 1b). Partial correlation coefficient analysis using status of surgery as the correction factor revealed positive correlations between hs-CRP and body weight (*r* = 0.374, *p* = 0.001, Fig. 1c) and BMI (*r* = 0.431, *p* < 0.001, Fig. 1d). Table 3 shows the results of the univariate and multivariate analysis. In the univariate analysis, ALT (β = 0.0034, *p* = 0.048) and hs-CRP (β = 0.3928, *p* = 0.008) levels were statistically significant. The multivariate analysis demonstrated that uric acid (β = -0.2173, *p* = 0.005), LDL-c (β = -0.0048, *p* = 0.045), and hs-CRP (β = 0.5364, *p* = 0.026) were independent risk factors influencing ACR.

Among the evaluated novel biomarkers, only serum leptin showed significant results, being significantly correlated with delta BMI (*r* = 0.481, *p* = 0.006, Fig. 2a), delta body weight (*r* = 0.439, *p* = 0.013, data not shown), and %TWL (*r* = 0.363, *p* = 0.045, data not shown). Receiver operating characteristic (ROC) curve was drawn, and area under the curve (AUC) was calculated to evaluate whether leptin predicted the degree of

Table 2 Changes of parameters at baseline and 6 months after bariatric surgery

Parameters	Baseline	After 6 months	<i>p</i> value
Body weight (kg)	98.9 ± 17.6	78.1 ± 14.8	< 0.001
BMI (kg/m ²)	36.9 (34.0–42.8)	29.5 (26.6–32.2)	< 0.001
SBP (mmHg)	124.9 ± 11.5	123.5 ± 11.7	0.720
DBP (mmHg)	79.5 ± 8.7	77.0 ± 7.4	0.140
WBC (/μL)	8544 ± 2194	6965 ± 1767	< 0.001
Hb (g/dL)	13.7 ± 1.1	12.9 ± 1.1	< 0.001
Platelet (10 ³ /μL)	276.9 ± 62.0	255.8 ± 57.1	< 0.001
Albumin (g/dL)	4.3 ± 0.3	4.3 ± 0.2	0.746
Glucose (mg/dL)	97 (87–119)	93 (87–103)	0.186
^a HbA1c (%)	7.7 ± 1.7	6.4 ± 0.9	0.006
AST (U/L)	27 (19–36)	19 (16–24)	< 0.001
ALT (U/L)	39 (23–63)	18 (12–24)	< 0.001
Total cholesterol (mg/dL)	194 (173–226)	183 (164–203)	0.032
LDL-c (mg/dL)	122.6 ± 35.2	114.9 ± 35.6	0.206
HDL-c (mg/dL)	46.4 ± 9.7	48.1 ± 10.5	0.205
Triglycerides (mg/dL)	144 (86–219)	86 (69–110)	< 0.001
Uric acid (mg/dL)	5.7 ± 1.3	5.1 ± 1.2	0.001
hs-CRP (mg/L)	0.39 (0.24–0.69)	0.09 (0.05–0.23)	< 0.001
Blood urea nitrogen (mg/dL)	11.60 ± 2.94	10.73 ± 3.12	0.065
Creatinine (mg/dL)	0.59 (0.53–0.71)	0.57 (0.51–0.63)	0.003
UACR (mg/g creatinine)	17.95 (6.81–72.89)	8.11 (4.67–15.92)	< 0.001
eGFR (ml/min/1.73 m ²)	115.7 ± 16.5	120.2 ± 12.6	0.003

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, WBC white blood cell, Hb hemoglobin, HbA1c glycated hemoglobin, AST aspartate aminotransferase, ALT alanine aminotransferase, LDL-c low density lipoprotein cholesterol, HDL-c high-density lipoprotein cholesterol, hs-CRP highly sensitive C-reactive protein, UACR urine albumin to creatinine ratio, eGFR estimated glomerular filtration rate

^a The value was measured only in patients with diabetes

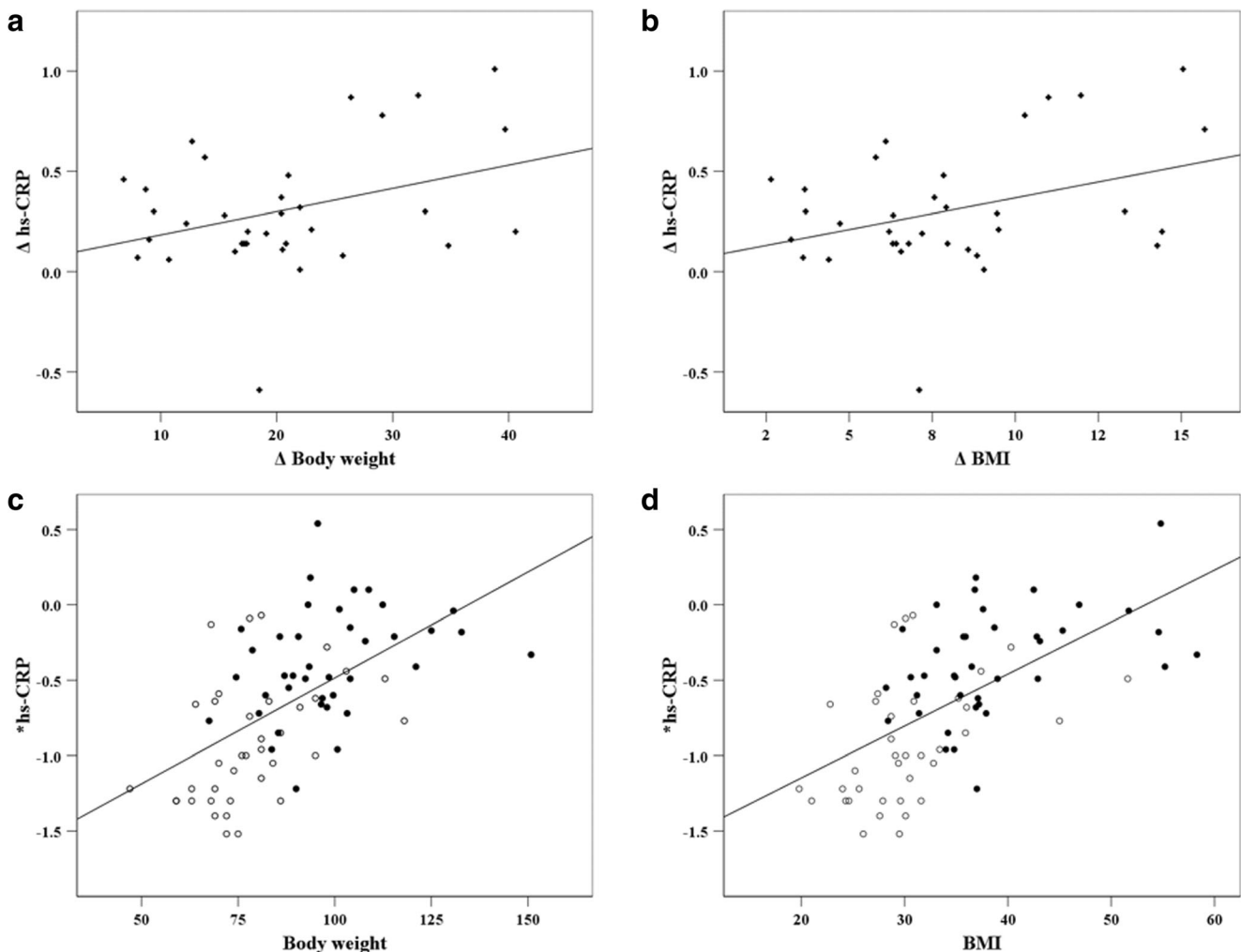


Fig. 1 Correlation plot between **a** delta hs-CRP and delta body weight ($r = 0.349$, $p = 0.043$), **b** delta hs-CRP and delta BMI ($r = 0.362$, $p = 0.035$), **c** hs-CRP and body weight ($r = 0.374$, $p = 0.001$), **d** hs-CRP and BMI ($r = 0.431$, $p = 0.001$). Note: white circles and black circles

denote the value measured before BS and after BS, respectively. Abbreviations: hs-CRP highly sensitive C-reactive protein, BMI body mass index. Asterisk indicates log-transformed value was used

BMI reduction after BS. Leptin level did predict decreased BMI > 25% and %TWL > 25% (cutoff value, 330 pg/mL; AUC, 0.756; sensitivity, 85.7%; specificity, 75.0%; $p = 0.042$, Fig. 2b; the two results were the same).

Discussion

BS greatly reduces body weight and BMI and is a treatment of choice in patients with severe obesity [5]. Weight loss is associated with improvements of systemic inflammation, renal function, and proteinuria [2, 3, 6]. Navarro et al. reported the long-term BS-related improvement of renal parameters, especially proteinuria and albuminuria, via weight reduction [12]. Another recently published study demonstrated that ACR and urine protein-to-creatinine ratio are improved after BS [21]. There is no doubt that weight loss leads to a reduction in albuminuria or proteinuria.

Given the previous studies, mechanisms of reduced proteinuria and albuminuria include improved blood pressure and glucose metabolism, and reduced systemic inflammation [18]. Improved systemic inflammation results in decreased albuminuria [22, 23]. However, it is unclear whether reduction of proteinuria is due to weight loss per se or improved systemic inflammation induced by weight loss. Agrawal et al. described the greater reduction in hs-CRP observed with more surgical weight loss [22]. The association between ACR and hs-CRP was analyzed using logarithmically transformed data without any consideration of other confounding factors that might affect albuminuria. Wiebke et al. reported that ACR and hs-CRP are concomitantly decreased by BS, but they focused more on renal and cytokines rather than the interconnection between systemic inflammation and albuminuria [23]. In the present study, hs-CRP and ACR levels were significantly decreased after BS, similar to previous studies (Table 2). The degree of reduction in BMI or body weight was significantly

Table 3 Effect of parameters on urine albumin-creatinine ratio: results of univariate and multivariate analysis using linear mixed model

Parameters	Univariate			Multivariate		
	β	95% CI	<i>p</i> value	β	CI	<i>p</i> value
Body weight	0.0041	− 0.0041–0.0123	0.325	0.0058	− 0.0189–0.0304	0.638
BMI	0.0097	− 0.0097–0.0291	0.319	− 0.0131	− 0.0711–0.0449	0.649
WBC	0.0000	0.0000–0.0001	0.201	0.0000	− 0.0001–0.0001	0.979
Hb	0.0646	− 0.0692 – 0.1984	0.338	0.1654	− 0.0159–0.3467	0.072
AST	0.0051	− 0.0010–0.0112	0.099	− 0.0059	− 0.0387–0.0269	0.719
ALT	0.0034	0.0000–0.0068	0.048	0.0064	− 0.0121–0.0249	0.488
LDL-c	− 0.0021	− 0.0064–0.0022	0.338	− 0.0048	− 0.0096– 0.0001	0.045
Triglycerides	0.0004	− 0.0008–0.0016	0.489	− 0.0004	− 0.0017–0.0009	0.541
Uric acid	− 0.0638	− 0.1814–0.0537	0.281	− 0.2173	− 0.3658– 0.0688	0.005
eGFR	− 0.0036	− 0.0140–0.0067	0.482	− 0.0052	− 0.0170–0.0066	0.374
^a hs-CRP	0.3928	0.1068–0.6787	0.008	0.5364	0.0678–1.0049	0.026
Diabetes	0.1811	− 0.1612–0.5233	0.290	0.1202	− 0.2754–0.5158	0.536

CI confidence interval, BMI body mass index, WBC white blood cell, Hb hemoglobin, AST aspartate aminotransferase, ALT alanine aminotransferase, LDL-c LDL cholesterol, eGFR estimated glomerular filtration rate, hs-CRP highly sensitive C-reactive protein

^aLog-transformed value was used

correlated with changes of hs-CRP (Fig. 1). Multivariate analysis revealed that hs-CRP is an independent risk factor influencing ACR, but BMI, body weight, and eGFR are not (Table 3). These results suggest that weight loss by BS directly improves systemic inflammation, which subsequently leads to reduced albuminuria via improvement of systemic inflammation, rather than the direct effect of weight loss. Interestingly, diabetes, as a factor for this univariate and multivariate model, did not show a statistical significance to reduce ACR after BS,

implying that the reduction in ACR was not affected by the presence of diabetes.

In this study, serum uric acid and ACR levels decreased after BS. However, multivariate analysis revealed uric acid as an independent risk factor that negatively affected ACR. The reason for this conflicting result may be because multiple confounding factors were taken into account in the multivariate analysis. An observational study reported the positive association of albuminuria with serum uric acid level and tubular

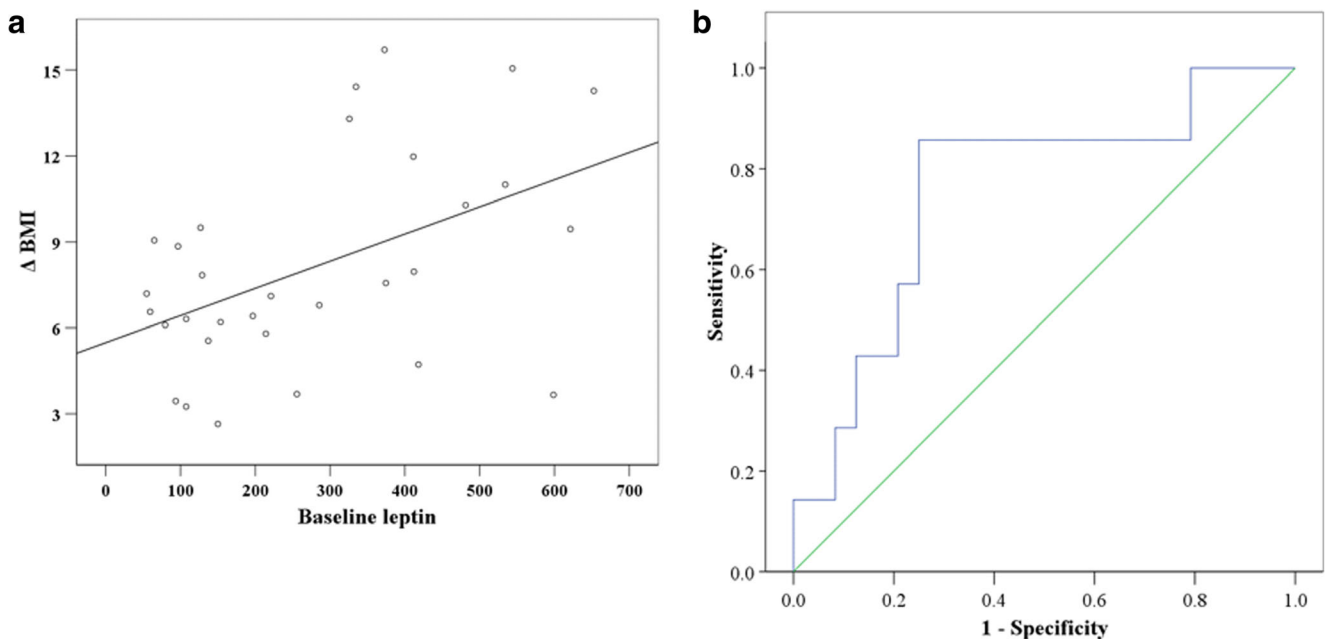


Fig. 2 **a** Baseline leptin level was correlated with delta BMI. **b** ROC curve showed the power of leptin to predict BMI reduction > 25% after BS (cutoff value 330 pg/mL, AUC 0.756, sensitivity 85.7%, specificity 75.0%, *p* = 0.042)

uric acid resorption [24]. Another study showed that uric acid and proteinuria were reduced after weight loss [19]. Thus, it is suggested that a decrease in uric acid after BS is likely to have a positive effect on the reduction of proteinuria. Consideration of our conflicting findings together with the previous results strongly indicates interrelated mechanisms between uric acid and albuminuria. Further studies are needed to evaluate the effect of uric acid on albuminuria. The effect of LDL-c on ACR shown by this study is problematic to interpret because β was too low (Table 3). Interpretation of this result is beyond the scope of this study. To explore the association of LDL-c with proteinuria, a more sophisticated study will be needed.

BS is a very effective treatment for weight loss in patients with severe obesity. In our study, BS induced significant weight loss. However, the changes of blood pressure after BS were not statistically significant. Prior studies have reported that BS decreases blood pressure by decreasing weight loss. The present findings may reflect the small number of hypertensive patients. Only 12 patients (27.3%) had hypertension, and all were taking anti-hypertensive medications. Their blood pressure before BS was stable. These reasons could explain the absence of significant change in blood pressure during the observation period. After BS, serum AST and ALT levels decreased and lipid profile improved, as previously reported. [5].

Leptin levels decrease after weight reduction [25]. Serum leptin level does not predict successful weight loss in patients with obesity [26], and this unpredictability is observed even in the patients received Roux-en-Y gastric bypass surgery [27]. In the present study, however, it was demonstrated that the patients with higher leptin level showed more reduction in BMI. The AUC value 0.756 indicates the potential value of leptin as a marker to predict the degree of weight reduction (Fig. 2). The reason for the inconsistent results from previous studies is unclear; however, the difference in male and female ratio might be the cause of conflicting result. Obese women who regain weight after weight loss have significantly lower baseline leptin than women who maintain weight loss [28], implying the leptin might play a certain role in pathophysiology of obesity, particularly in obese women. In this study, the female was proportionally predominant in number than the previous study (93% vs. 57%).

There are some limitations in this study. It is difficult to say that the patients in our study represented all obese Koreans, since those who wanted BS were participated. In addition, the proportion of patients with hypertension was low (27.3%). Evaluation of the effect on hypertension was not performed because it was not the main objective of our study. Another limitation was the method to measure the degree of albuminuria and to determine GFR. Albuminuria was assessed using spot ACR, not 24-h urine. GFR was determined using the CKD-EPI equation, not 24-h creatinine clearance. However, random urine and CKD-EPI equation have been used before

[13]. We included patients with BMI ≥ 30 kg/m² because, in Asians, these people are considered obese (obesity II classification), corresponding to BMI ≥ 35 kg/m² in Caucasians [19].

In conclusion, BS can reduce albuminuria in patients with severe obesity and normal kidney function by reducing systemic inflammation.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflicts of interest.

Ethical Statement and Consent Statement The study protocol was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (IRB No. SCHCA_IRB_2011-78). All patients provided their written informed consent.

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