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SHORT TERM EFFECT OF LAPAROSCOPIC SLEEVE GASTRECTOMY ON CLINICAL, RENAL PARAMETERS AND URINARY NGAL LEVELS IN DIABETIC AND NON DIABETIC OBESITY

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Abstract

Background. Although diseases such as diabetes, hypertension, obstructive sleep apnea and hyperlipidemia are clearly documented as obesity associated diseases, it is not well-known whether obesity causes renal pathologies. The aim of the present study was to evaluate the effect of weight loss following laparoscopic sleeve gastrectomy on clinical, renal parameters and urinary Neutrophil gelatinase-associated lipocalin (NGAL) levels in diabetic and non-diabetic obese patients.

Methods. Nineteen morbidly obese patients (10 diabetic and 9 non diabetic) who underwent laparoscopic sleeve gastrectomy were evaluated clinically (anthropometric measurements) and biochemically before surgery and at 6 months from surgery.

Results. Significant decreases in weight, BMI, FPG, PPG and HbA1c levels were observed in the diabetic group when the baseline and 6th month parameters of the patients were compared. There was also a significant decrease in SBP and DBP. At 6th month following laparoscopic sleeve gastrectomy, renal parameters such as creatinine, mAlb/creatinine, NGAL/creatinine did not differ in the diabetic group. In the nondiabetic group, serum creatinine levels were significantly decreased, but other renal parameters such as mAlb/creatinine and NGAL/creatinine were not significantly different.

Conclusions. Our findings revealed significant decreases in weight, body mass index and glycemic parameters after sleeve gastrectomy in diabetic and non-diabetic patients, while no significant alteration was noted in renal functions, urinary NGAL and microalbumin levels.

Key words: sleeve gastrectomy, obesity, urinary NGAL, kidney, weight loss, T2DM.

INTRODUCTION

Although diseases such as diabetes, hypertension, obstructive sleep apnea and hyperlipidemia are clearly documented as obesity associated diseases, it is not well-known whether obesity causes renal pathologies. Some studies have shown that obesity leads to glomerular hyperfiltration. However underlying mechanisms are not clear (1). Neutrophil gelatinase-associated lipocalin (NGAL), a polypeptide expressed in neutrophils and various epithelial cells, is a valuable marker that can indicate acute and chronic renal diseases (2). It is also an early biomarker of diabetic nephropathy (3). In a healthy kidney, minimal NGAL synthesis is seen only in the distal tubular epithelium and in the collecting channels in the medullary region. However, 50% of the cortical tubules in the damaged kidneys due to ischemia or nephrotoxic agents have been reported to express NGAL (4-6).

There are contradictory reports on NGAL levels in obesity. Wang *et al.* showed that NGAL is closely related to obesity and its metabolic complications (7). Yan *et al.* found that NGAL level is significantly higher in obese mice (8). Similarly, urinary NGAL level has been reported to be significantly increased in obese children (9) and there is higher NGAL protein expression in the visceral fat deposit of obese patients (10). However, in another study, it was demonstrated that the level of urinary NGAL was not significantly different between the obese and non-obese group (11). In addition, Wang *et al.* showed that NGAL is associated closely with insulin resistance and hyperglycemia (7). In type 2 diabetic patients ranging from normo-albuminuria group to macro-albuminuria group, urine NGAL levels tended to increase (12).

The aim of the present study was to evaluate the effect of weight loss following laparoscopic sleeve gastrectomy (LSG) on the clinical, renal parameters and urinary NGAL levels in diabetic and non-diabetic obese patients.

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PATIENTS AND METHODS

All procedures in this clinical trial were carried out in accordance with the ethical principles and standards in the recently revised Declaration of Helsinki. The local ethics committee approved the study protocol. The written consent of the participants was obtained prior to enrolment. This prospective study was planned for 25 morbidly obese patients between the ages of 18-65 admitted to Endocrinology and Metabolism outpatient clinic between January 2011 and December 2015 for bariatric surgery. Patients who did not attend their follow-up visits in the postoperative period were excluded from the study, and the remaining 19 patients (10 diabetic, 9 nondiabetic) were analysed and divided into the diabetic and non-diabetic group.

Laparoscopic sleeve gastrectomy was performed as bariatric surgery. Sleeve gastrectomy, which is a volume-restrictive method, is a type of partial gastrectomy that removes most of the large curvature of the stomach and gives the stomach a tube shape. In this study basic techniques of LSG were performed in accordance with literature. These included gastrectomy beginning 2 m to 6 cm proximal to the pylorus (for pyloric preservation), mobilization of the entire greater curvature and identification of the left crus and base of the right crus, proper apposition of the anterior and posterior aspects of the stomach when stapling to prevent a corkscrewing effect of the sleeve.

Patients who underwent laparoscopic sleeve gastrectomy were evaluated clinically and biochemically in the preoperative and postoperative 6 months period. Anthropometric measurements such as height and weight, blood pressure arterial measurements [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] were performed. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Following 8-10 hours of fasting, fasting plasma glucose (FPG), Hemoglobin A1c (HbA1c), creatinine, alanine aminotransferase (ALT), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC) values were measured. HbA1c level was measured in the blood sample collected in an ethylenediamine tetraacetic acid tube. Homeostasis model assessment of insulin resistance (HOMA-IR) value was calculated by using fasting glucose x insulin/405 formula in non-diabetic patients. Estimated Glomerular Filtration Rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculator, which used creatinine, age, sex, and race parameters. We defined the presence and stages of chronic kidney disease using the urinary albumin/creatinine ratio with eGFR. Serum samples were immediately studied, and samples obtained for urinary albumin and NGAL measurements were stored at -80ºC until the day of the analysis. Concentrations of serum glucose, urea, total protein, albumin, TC, HDL-C, TG, creatinine and urine creatinine were measured via photometric methods using the Abbott brand kit on an Architect C16000 instrument. HbA1c level was measured by boronate affinity chromatography using the Premier Hb9210 (Trinity Biotech) device.

Urine albumin concentrations were measured by immunoturbidimetry using the Abbott analyzer. Urinary NGAL measurements were performed on an Architect i2000 using the Abbott brand kit, which utilizes the chemiluminescent microparticle immunoassay method. The ratio of NGAL/creatinine (µg/mg) was used as the ratio of measured urine NGAL concentration (ng/mL) to urine creatinine (mg/dL). Coefficients of variation (CV%) were found to be 4.07% and 4.08% in the reproducibility study of the sample pool containing NGAL at normal (mean 5.25 ng/mL) and high (154.9 ng/mL) levels, respectively.

Statistical analysis

In the present study, whether the data were distributed normally was tested with Shapiro-Wilk test. In comparing the data with normal distribution between two independent groups, the independent sample t-test was used and the non-normal distribution of the data between two independent groups was evaluated with the Mann-Whitney U test. McNemar test was used to compare dependent categorical variables. In paired group comparisons, paired T-test was used in the case of normal distribution of data, and Wilcoxon signal row test was used when the data were not normally distributed. Parameters with normal distribution are presented as the mean ±standard deviation, and non-parametric variables are expressed with median (minimum-maximum). Categorical variables are given with n (%) values. All statistical analyses were performed at IBM Spss Statistics 21 program with a significance level of 0.05 and 95% confidence level.

RESULTS

The preoperative clinical and biochemical features of the patients were shown in Table 1. There were no significant differences between the groups in

terms of age, gender, weight, BMI. Nine patients in the diabetic group used oral antidiabetic (OAD) while 4 patients used insulin. The mean insulin dose was 0.678 (0.4-1.07) units/kg/day in patients using insulin. The mean HOMA-IR in the nondiabetic group was found to be 1.98 (0.64-20.26). While the mean FPG, PPG and HbA1c values were significantly higher in the diabetic group, there were no significant differences between the two groups in terms of other parameters.

At the postoperative sixth month, mean serum HbA1c, LDL-C, TC and creatinine levels were significantly higher in the diabetic group. But no significant difference was observed between the groups in terms of other parameters (Table 2). In postoperative period it was observed that 4 patients continued to use OAD and 2 patients continued to use insulin. The mean insulin dose was 0.337 (0.17-0.5) units/kg/day in the sixth month.

Significant decreases in weight, BMI, FPG, PPG and HbA1c levels were observed in the diabetic group when the baseline and 6th month parameters of the patients were compared. There was also a significant decrease in SBP and DBP. While there was a significant decrease in use of OAD, there was no significant difference in use of insulin. Renal parameters such as creatinine, mAlb/creatinine, NGAL/creatinine were not significantly different (Table 3). In the nondiabetic group, weight loss, BMI, HOMA-IR, FPG and HbA1c were significantly lower in the 6th month than in baseline. There was a significant decrease in serum creatinine levels and a significant increase in GFR values in this group. Other renal parameters such as mAlb/creatinine and NGAL/creatinine were not significantly different.

On the third postoperative day, stapler line leakage was observed in one patient and the patient was reoperated. After re-operation the patient continued to be followed-up without any problem. In another patient new-onset gastroesophageal reflux disease occurred and it was controlled with medical treatment.

DISCUSSION

Obesity-related renal damage, which has frequently been emphasized in the recent period, is a condition with glomerular hyperfiltration but

Table 1. Initial demographic and laboratory features of the patients participating in the study

	Diabetic (n=10)	Non-diabetic (n=9)	p
Age (year)	45.7±10.4	37.56±7.5	0.071
Gender (F/M)	6/4	7/2	0.628
Duration of diabetes(year)	4.50±2.27	-	-
Weight (kg)	128.30±16.18	133±24.74	0.627
BMI (kg/m^2)	46.563±5.33	49.88±6.16	0.225
OAD usage(n)	9 (%90)	-	-
Insulin usage(n)	4 (%40)	-	-
Insulin dosage/weight (unit/kg/day)	0.678(0.4-1.07)	-	-
HOMA-IR	-	1.98(0.64-20.26)	-
SBP (mmHg)	132.5 (120-177)	125.56±17.04	0.243
DBP (mmHg)	80 (70-104)	80 (60-93)	0.447
FPG (mg/dL)	167.9±56.07	98±15.25	**0.003**
PPG (mg/dL)	199±59.23	113.67±16.47	**0.001**
HbA1c (%)	7.03±0.95	6.11±0.20	**0.014**
ALT (IU/L)	33.5 (17-90)	25 (12-99)	0.400
LDL-C (mg/dL)	141.9±53.73	111.56±19.34	0.122
HDL-C (mg/dL)	41.5 (22-58)	40±5.408	0.940
TG (mg/dL)	179.8±85.49	139.44±38.49	0.201
TC (mg/dL)	218.3±56.12	182.11±23.03	0.085
Creatinine (mg/dL)	0.877±0.22	0.690 (0.6-1.9)	0.079
eGFR (mL/min/1.73 m^2)	94.35 (46.3-126.3)	109.90 (44.3-123)	0.113
Chronic kidney disease(n)	3 (30%)	1 (11.1%)	0.582
Urine mAlb	5 (5-283)	5 (5-36)	0.968
Urine mAlb/cre	8.299 (2.87-149.25)	4.03 (2.41-29.23)	0.315
NGAL	13.05 (1.9-64.8)	25.7 (10.7-538.2)	0.113
NGAL/cre	10.58 (1.15-44.16)	14.05 (8.19-328.19)	0.166

BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance,SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG:fasting plasma glucose, PPG:postprandial plasma glucose, HbA1c: Hemoglobin A1c, ALT: alanine amino transferase, LDL-C:low density lipoprotein cholesterol, HDL-C:high density lipoprotein cholesterol, TG:triglyceride, TC: total cholesterol, eGFR: Estimated Glomerular Filtration Rate, mAlb: microalbumin, cre: creatinine, NGAL: Neutrophil gelatinase-associated lipocalin.

Table 2. Demographic and laboratory features of patients in the postoperative 6th month

	Diabetic (n=10)	Non-diabetic (n=9)	p
Weight (kg)	94±13.34	99.22±19.60	0.513
BMI (kg/m²)	34.160±5.12	37.078±4.03	0.189
OAD usage (n)	4 (%40)	-	-
Insulin usage (n)	2 (%20)	-	-
Insulin dosage/weight (unit/kg/day)	0.337 (0.17-0.5)	-	-
HOMA-IR	-	0.67(0.08-1.39)	**-**
SBP (mmHg)	122.5 (110-140)	117.22±10.34	0.095
DBP (mmHg)	80 (70-80)	75 (60-80)	0.278
FPG (mg/dL)	111.3±32.08	85.22±11.34	**0.022**
PPG (mg/dL)	123.6±27.85	105.22±14.0	0.092
HbA1c (%)	5.91±0.71	5.22±0.42	**0.022**
ALT (IU/L)	20.5 (6-82)	16 (9-65)	0.549
LDL-C (mg/dL)	153.6±36.01	106.33±18.66	**0.003**
HDL-C (mg/dL)	41.5 (34-81)	38.11±8.16	0.356
TG (mg/dL)	145±56.12	115±29.95	0.163
TC (mg/dL)	226.7±47.39	169.89±23.12	**0.005**
Creatinine (mg/dL)	0.803±0.14	0.62 (0.5-1.6)	**0.035**
eGFR(mL/min/1.73 m²)	98.90 (79.5-127)	115 (52.7-127.1)	0.053
Chronic kidney disease(n)	2 (20%)	3 (33.3%)	0.628
Urine mAlb	10.5 (5-838)	9 (5-544)	0.549
Urine mAlb/cre	8.583 (2.64-686.6)	5.58 (1.89-316.28)	0.780
NGAL	22 (4.3-221.3)	32 (5.3-202.7)	0.315
NGAL/cre	15.778 (1.86-97.5)	12.914 (2.02-73.66)	0.842

BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: Hemoglobin A1c, ALT: alanine aminotransferase, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglyceride, TC: total cholesterol, eGFR:Estimated Glomerular Filtration Rate, mAlb: microalbumin, cre: creatinine, NGAL: Neutrophil gelatinase-associated lipocalin.

Table 3. Percentage changes (Δ) of the initial and 6th month values of clinical and laboratory parameters in diabetic and non-diabetic groups

	Δ Diabetic	p_x	Δ Non-diabetic	p_y	p_z
Weight (kg)	-26.38±8.41	**<0.001**	-25.06±7.88	**<0.001**	0.730
BMI (kg/m²)	-26.48±8.18	**<0.001**	-25.14±8.12	**<0.001**	0.726
OAD usage (n)	3(%50)	**0.031**	-	-	**-**
Insulin usage (n)	2(%50)	0.133	-	-	**-**
HOMA-IR	-	**-**	-0.66 (-0.96 - 0.77)	**0.011**	-
SBP (mmHg)	-0.08 (-0.21 - 0)	**0.018**	-0.04 (-0.29 - 0)	0.127	0.315
DBP (mmHg)	-0.07±0.096	**0.044**	-0.05±0.107	0.168	0.708
FPG (mg/dL)	-40.45 (-56.47 -53.33)	**0.022**	-11.54(-28.97 - 14.71)	**0.015**	0.095
PPG (mg/dL)	-34.01±19.80	**0.003**	-5.88±17.56	0.210	**0.005**
HbA1c (%)	-14.6±15.33	**0.016**	-14.58±5.74	**<0.001**	0.997
ALT (IU/L)	-0.37 (-0.82 - 1.48)	0.139	-0.17(-0.84 - 0.41)	**0.020**	0.382
LDL-C (mg/dL)	9.04 (-9.13 - 56.52)	0.247	-4.24 (-32.79 - 34.38)	0.476	0.400
HDL-C (mg/dL)	12.79±30.61	0.362	-4.36±18.05	0.471	0.161
TG (mg/dL)	-12.57±28.84	0.108	-16.03±15.3	**0.036**	0.752
TC (mg/dL)	0.65 (-9.18 - 35.38)	0.369	-2.6 (-30.81 - 15.89)	0.178	0.079
Creatinine (mg/dL)	-0.06±0.16	0.260	-0.07±0.1	**0.036**	0.851
eGFR(mL/min/1.73m²)	0.047 (-0.24 - 0.81)	0.123	0.041(-0.03 - 0.19)	**0.036**	0.720
UrinemAlb	0.09 (-0.89 - 166.6)	0.446	0.6 (-0.75 - 107.8)	0.128	0.400
UrinemAlb/cre	0.03 (-0.91 - 200.5)	0.575	0.45 (-0.94 - 130.2)	0.214	0.780
NGAL	0.19 (-0.7 - 13.95)	0.646	-0.21 (-0.91- 3.54)	0.441	0.356
NGAL/cre	-0.14(-0.77 - 12.12)	0.799	-0.24 (-0.94 - 2.43)	0.086	0.243

BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, PPG: postprandial plasma glucose, HbA1c: Hemoglobin A1c, ALT: alanine aminotransferase, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglyceride, TC: total cholesterol, eGFR:Estimated Glomerular Filtration Rate, mAlb: microalbumin, cre: creatinine, NGAL: Neutrophil gelatinase-associated lipocalin.

px: Comparison of initial and 6th month parameters in diabetic group; py: Comparison of initial and 6th month parameters in nondiabetic group; pz: Δ diabetic and Δ non-diabetic comparison.

its pathophysiology is still unclear. Functional and structural renal abnormalities including increased glomerular filtration rate and urinary albumin excretion are seen in obese individuals (13). In a study conducted by Navarro-Diaz *et al.* it was found that extremely obese patients had greater proteinuria and albuminuria compared to the control group (14). Unlike the results in these studies, Lurbe *et al.* investigated urinary albumin excretion in obese children and adolescents, and a statistically significant difference was not found when the groups at varying degree of obesity were compared (15). In another study, it was demonstrated that obesity per se does not exert an effect on urinary albumin excretion, but in obese individuals, blood pressure is a strong determinant of the level of urinary albumin (16).

There are contradictory reports on NGAL levels in obesity. Wang *et al.* demonstrated that circulating lipocalin-2 concentrations were positively correlated with BMI, waist circumference and fat percentage. In this study, it was also reported that lipocalin-2 concentrations were associated with fasting glucose concentrations, hyperinsulinemia, and HOMA-IR (7). Similarly, in obese children, urinary NGAL levels were found to be significantly higher and the authors concluded that NGAL could be used as a biomarker for assessing the renal effect of obesity (9). However, there are studies reporting no difference between obese and lean patients in this respect (11). In a study conducted by Yang *et al.* it was investigated whether NGAL could be a marker in determining diabetic nephropathy progression and the authors found that NGAL correlates closely with renal function (12).

In a study performed by Magalhaes *et al.* urinary albumin creatinine ratio was significantly decreased following the weight loss with bariatric surgery and significant predictors affecting urinary albumin excretion were body mass index, systolic blood pressure and HbA1c (17). Serra *et al.* showed that after bariatric surgery albuminuria and creatinine clearance significantly improved in extremely obese patients in the first year after surgery (18). Navarro-Diaz *et al.* also stressed that during the 2nd year of follow-up, albuminurea continued to decrease (14). In the present study, in the nondiabetic group, weight loss, BMI, HOMA-IR, FPG and HbA1c were significantly lower in the 6th month than in baseline. Serum creatinine levels were decreased while eGFR levels increased significantly following weight loss, but there was no significant change in mAlb/creatinine ratio. In the diabetic group, there was no significant difference in terms of creatinine and mAlb/creatinine between baseline and postoperative 6th month. But, there are important limitations of this study. One of these, a small number of patients could be included, causing limited statistical power analyses. Similarly, due to the small number of patients with chronic kidney disease, no statistical evaluation could be made between patients with or without chronic kidney disease. Another issue is that the follow-up in our hospital was terminated in the first postoperative year due to the desire of the patients to continue their follow-up to their primary physicians. Therefore, the fact that we cannot have data about the long-term outcomes of the patients is another limitation of the study.

The studies evaluating the relationship between bariatric surgery and urinary NGAL levels are limited in the literature. Koukoulaki *et al*. evaluated the effect of NGAL on acute kidney injury and observed that urinary NGAL levels increased before serum creatinine elevation in the first 24 hours after biliopancreatic diversion in patients with acute kidney injury (19). The comparison of NGAL levels with diabetic and non-diabetic patients after bariatric surgery is the strength of our study.

In conclusion, our findings revealed significant decreases in weight, body mass index and glycemic parameters at 6th month after sleeve gastrectomy in diabetic and non-diabetic patients, while no significant alteration was noted in renal functions, urinary NGAL and microalbumin levels. Further investigations would be helpful to elucidate the role of urinary NGAL levels in obesity.

Conflict of interest

The authors declare that they have no conflict of interest.

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