The Impact of the Pre-operative Neutrophil-lymphocyte Ratio as the Predictive Marker of Post-operative Weight Loss and Improving Diabetes in Sleeve Gastrectomy.

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Research article

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Abstract

Background: The aim of this study was to investigate the impact of the neutrophil-lymphocyte ratio (NLR) in sleeve gastrectomy (SG).

Methods: 15 obese patients were enrolled in this study. They consisted of 5 males and 10 females: mean body weight (BW) 127.5kg; mean body mass index (BMI) 46.7kg/m2. 10 of these were diabetics who underwent a SG. The impact of the pre-operative NLR on the percentage of excess weight loss (%EWL) and remission of diabetes 1 year post-operative were examined.

Results: The BMI, %EWL and %TWL at 1 year post-operative were 35.1 kg/m2, 46.3% and 26.2%, respectively. Improvements were also evident in the diabetes at 1 year post-operative: complete remission (CR) (No medication and hemoglobin A1c (HbA1c) HbA1c<6.0%) 40%, PR (HbA1c<6.5) 20%; and (decrease of anti diabetic drug and HbA1c<7.0%) 40%. Comparing pre-operative NLR in %EWL<50% and ≥50% in one (1) year post-operative, <50% was 2.64 and ≥50% was 2.03 ($p<0.05$). The NLR in CR and partial remission (PR) was significantly lower than that in improved (Improve) (2.22 vs 3.27, $p<0.05$).

Conclusions: The pre-operative NLR may be a predictive marker of weight loss and improving diabetes after SG.

Background

Metabolic syndrome (MS) is characterized by obesity, diabetes, hypertension (HT) and hyperlipidemia (HL). The incidence of MS has increased along with rapid economic development and an associated change in diet [1]. Consequently, increased attention has been paid to the prevention of MS.

There is strong evidence that bariatric surgery is an effective treatment to keep the long-term weight loss [2–4]. Several reports have shown that bariatric surgery is superior to internal medicine in the treatment of MS [5]. Especially, bariatric surgery has been reported to accomplish complete remission in obese patients with Type 2 diabetes mellitus (T2DM) [6].

The authors have previously reported that duodenal-jejunal bypass (DJB) improved T2DM and liver steatosis by enhanced glucagon like peptide-1 (GLP-1) secretion through increase of bile acids and the proliferation of L cells in the ileum [7].

The laparoscopic sleeve gastrectomy (LSG) was initially used at a stage prior to duodenal switch or gastric bypass in the patients with high surgical risk. Recently, this procedure has a popularity due to the good short-term outcomes and its relatively lower technical difficulties [8, 9]. In Japan, the number of the obese patients who have undergone LSG has been increasing [10].

Obesity and MS were reported to show the disruption of lymphoid tissue integrity, alterations in leukocyte development, and the co-ordination of innate and adaptive immune responses [11]. So, the state of obesity showed impaired immunity.

The neutrophil-to-lymphocyte ratio (NLR) is an available inflammatory marker to predict complications following a variety of major surgical procedures [12–14]. Regarding the correlation between the NLR and bariatric surgery, Da Silva M, et al. reported that the post-operative one (POD1) NLR was associated with thirty (30) day outcomes in LSG [15]. However, the relationships between the NLR and long-term outcomes remains unclear.

The aim of this study was to investigate the impact of the NLR regarding post-operative weight loss and improving diabetes in sleeve gastrectomy (SG).

Methods

Patient selection and data collection

Patients were included in this study based on the following indicators: a LSG at the Tokushima University Hospital; aged between eighteen (18) years and sixty (60) years; a body mass index (BMI) of > 35 kg/m2; internal therapy of > 6 months; and co-morbidity with T2DM, HT, HL or sleep apnea syndrome (SAS).

The exclusion criteria were: known malignancies; pregnancy; and conditions associated with poor compliance (psychiatric illness).

The protocol for this research project was approved by a suitably constituted Ethics Committee of the Tokushima University Hospital (ToCMS:3215).

From 2013 to 2018, fifteen (15) patients (five (5) males and ten (10) females; age range from thirty-three (33) years to fifty-six (56) years (mean age 42.7 years); and a mean BMI of 46.7) were referred to the Tokushima University Hospital for treatment of morbid obesity. There were thirteen (13) patients who underwent a LSG. There was no cases with conversion to open SG in these 13 patients. Co-morbidity included the following: ten (10) patients with T2DM; eleven (11) patients with HT; six (6) patients with HL; and eleven (11) patients with SAS. A mean hemoglobin A1c (HbA1c) was 6.6 (4.9–8.5).

Data were collected retrospectively from medical records and supplemented with data and laboratory results.

Technical description of an LSG

“The surgical techniques for the LSG procedures have been previously published [31].” In brief, using 5-port laparoscopic technique, LSG was performed. The greater curvature and the angle of His were dissected to staple the gastric fundus and greater curvature parallel to a gastric fiber, which was inserted in the stomach through the esophagus. The bougie was not used in our procedure. Stapling (total five (5) to eight (8) times) was started from a distance of 5 cm to 8 cm from the pylorus on the greater curvature side toward the angle of His. This resulted in a tube-like stomach with a volume of approximately 100 mls made from the lesser curvature only. The staple line was reinforced by 3 – 0 PDS and vicryl continuous sutures. In case of suspected severe adhesion preoperatively, open SG was selected in our department. In this series, two (2) cases underwent open SG, because of previous upper abdominal operations.

NLR, prognostic nutritional index (PNI) and ABCD score

The NLR and PNI were calculated pre-operative and three (3) months post-operative. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The PNI was calculated as described previously [16]; briefly, PNI=[10 × albumin (g/dl)]+[0.005 × total lymphocyte count (μl)]. The ABCD score was composed of the patient's age (A), body mass index (B), C-peptide level (C), and duration of T2DM (years) (D) [17]. In this study, the remission of T2DM after SG was evaluated using the ABCD score.

Evaluation of T2DM resolution

The resolution of T2DM was evaluated using the patient data at twelve (12) months after surgery. Complete remission (CR) was defined as no medication required and HbA1c < 6.0%, partial remission (PR) as no medication required and HbA1c < 6.5%, improved (Improve) as medication reduced and HbA1c < 7.0% and no change (NC) as HbA1c ≥ 7.0%, regardless of medication [18].

Post-operative management

After the SGs, the patients were started with water on day (1) post-operative and a liquid diet on days four (4) or five (5) post-operative. A thrombosis prophylaxis was administered twice a day for a week.

After discharge, the patients were followed up once at one (1) or two (2) months. At outpatient's clinic, the body weight (BW), blood test and the state of obesity-related disease in the patients were evaluated. The percent excess weight loss (%EWL) and percent total weight loss (%TWL) were checked at one (1) year post-operative. Excess weight was defined as the subject's baseline weight minus the ideal weight that would equate to a BMI of 22.

Statistical analysis

The t-test was used for statistical analysis of the continuous variables. For all tests, $p < 0.05$ was interpreted as significant. The values for each continuous variable were expressed as a mean ± the standard deviation (SD).

Results

An overview of the long-term outcomes after the LSGs is given in Table 1. The BMI, %EWL and %TWL in one (1) year post-operative was 35.1 kg/m2 (30.6–44.4), 46.3% (35.5–62.6), and 26.2% (14.3–38.9), respectively. Regarding the resolution of T2DM, there were 40% of patients in CR, 20% in PR, and 40% in Improve. HbA1c at one (1) year post-operative was significantly lower than that at pre-operation (6.6 vs 5.7, $p < 0.05$). Other obesity related diseases: HT 64%; HL 67%; and SAS; 91% had also improved at one (1) year post-operative. The NLR at three (3) months post-operative was significantly lower than that at pre-operation (2.53 vs 1.84, $p < 0.05$) (Fig. 1a). Comparing the pre-operative NLR in %EWL < 50% and ≥

50% at one (1) year post-operative, $< 50\%$ was 2.64 and $\geq 50\%$ was 2.03 ($p < 0.05$) (Fig. 1b). In addition, the preoperative NLR in 30%≤%TWL was lower than that in 30%>%TWL at postoperative one (1) year (2.89 vs 2.15, $p = 0.09$) (Fig. 1c). However, other pre-operative factors did not correlate with the %EWL at one (1) year post-operative (Table 2). Regarding the resolution of T2DM, the NLR in CR and PR was significantly lower than that in Improve (2.22 vs 3.27, $p < 0.05$) (Fig. 1d). Other pre-operative factors including the ABCD score did not correlate with the resolution of T2DM at one (1) year post-operative (Table 3). In our bypassed case, a diabetic obese patient with preoperative NLR 3.84 and ABCD score 6 (Preoperative BMI: 38.4 kg/m2, HbA1c: 11.0%) showed 75.5% in %EWL and CR in DM remission in postoperative 1 year after laparoscopic sleeve gastrectomy with bypass. So, preoperative NLR was effective in the selection of operative procedure (SG or bypass).

Table 1
Long-term outcome after SG.

Factors	**n = 15**
BMI in postoperative 1 year	35.1 kg/m2 (30.6–44.4)
%EWL in postoperative 1 year	46.3% (35.5–62.6)
%TWL in postoperative 1 year	26.2% (14.3–38.9)
Improvement of obesity-related disease	T2DM; CR 40%/ PR 20%/ Improve 40%
in postoperative 1 year	Hypertension 64%
	Hyperlipidemia 67%
	Sleep apnea syndrome 91%
HbA1c (%) in postoperative 1 year	5.7 (4.8–7.0)

Table 2
The relationships between preoperative factors and %EWL

Preoperative factors	%EWL in postoperative 1 year		p value
	< 50%	50%≤	
Age (y.o.)	42.5 ± 7.5	42.4 ± 7.8	0.98
Gender (male/ female)	3/ 5	2/ 3	0.93
BW (kg)	124.4 ± 26.3	135.8 ± 21.3	0.47
BMI (kg/m^2)	46.1 ± 8.3	49.6 ± 7.1	0.49
Diabetes (+/ -)	5/ 3	3/ 2	0.93
ABCD score	4.20 ± 0.75	5.33 ± 1.25	0.37
NLR	2.64 ± 0.60	2.03 ± 0.17	< 0.05
PNI	49.7 ± 4.7	45.1 ± 6.5	0.25

Table 3
The relationships between preoperative factors and resolution of T2DM

Preoperative factors	Resolution of T2DM in postoperative 1 year		p value
	CR/ PR	Improve	
Age (y.o.)	41.5 ± 4.9	43.8 ± 5.4	0.56
BW (kg)	130.8 ± 22.0	109.0 ± 19.5	0.19
BMI (kg/m^2)	45.5 ± 8.1	40.1 ± 3.5	0.30
HbA1c (%)	7.4 ± 0.8	7.5 ± 0.8	0.96
C peptide (ng/ml)	2.93 ± 1.41	4.02 ± 1.11	0.39
ABCD score	4.67 ± 1.89	4.5 ± 0.5	0.88
NLR	2.22 ± 0.36	3.27 ± 0.74	< 0.05
PNI	51.8 ± 1.92	48.0 ± 7.80	0.34

Discussion

This study was designed to investigate the impact of the pre-operative NLR as the predictive marker of post-operative weight loss and improving diabetes in SG.

A SG, in which 80% of the stomach is removed along the greater curvature but the intestinal anatomy is unchanged, has been gaining in popularity. A SG is considered as a definitive procedure for the treatment of morbid obesity and obesity-related diseases. The number of SGs has been increasing in many countries [19–21]. A SG is successfully performed by laparoscopy in 99.7% of cases, with relative safety [22].

The resolution rates of obesity-related diseases in LSG were reported for: diabetes (58.6%); HT (38.8%); HL (63%); and SAS (91.2%) [23]. Regarding the postoperative weight loss, %EWL in postoperative 1 year showed less than 50%. As one of the reasons, preoperative BMI was relatively high (average BMI; 46.7) and the ratio of super-obese patients (BMI > 50 kg/m2) was 40% (6 / 15).

A previous report discussed the mechanism of improving T2DM in bariatric surgery, duodenal-jejunal bypass (DJB) enhanced GLP-1 secretion through increased bile acids and the proliferation of L cells [7]. The authors also reported that DJB changed the composition of gut microbiota and these changes might contribute to some of the benefits of DJB [24]. Ryan KK, et al. reported that bile acids and the bile acid receptor, known as the farnesoid X receptor (FXR) were important molecular targets for the beneficial effects of bariatric surgery [25].

The ABCD score has been well-known as a predictor of the success of T2DM treatment after LSG. In this report, the authors would only recommend LSG for the T2DM patients with an ABCD > 4 [17]. Regarding the predictor of post-operative weight loss after LSG, Seki, et al. reported that the %EWL in the super morbid obesity group (50 ≤ BMI) was significantly lower than that in the mild obesity group (BMI < 35) and reference group (35 ≤ BMI < 50) [26]. However, the ABCD score and pre-operative BMI have no relationship with the resolution of T2DM and post-operative weight loss in the authors’ study. In that study, a low pre-operative NLR correlated with the improvement of T2DM and %EWL ≥ 50 in one (1) year post-operative in SG. Therefore, the pre-operative NLR may be the only predictive marker of post-operative weight loss and improving T2DM in SG.

A high fat diet elevated the intestinal inflammatory cytokine, alongside compromised mucosal barrier integrity with a loss in the tight junction protein (claudin-1) and increased the severity of colitis, which leads to insulin resistance due to inflammation of the liver and adipose tissue [27]. The authors reported that DJB surgery maintained gut permeability through the suppression of gut inflammation. Therefore, DJB might improve insulin resistance by the suppression of inflammation in insulin-target tissue such as the liver and adipose tissue [28]. The role of the NLR was reported to be a marker of intestinal inflammation because it reflected changes in the gut microbiota [29]. Nlrp3 inflammasome sensed the obesity–associated danger-signals and contributed to the obesity–induced inflammation and insulin–resistance [30]. So, the state of pre-operative inflammation may correlate with post-operative weight loss and glucose tolerance. Therefore, the pre-operative NLR may reflect pre-operative intestinal and systemic inflammation and contribute to post-operative weight loss and the resolution of T2DM in SG.

Our study had the limitation that this was not a long-term result especially for weight loss and reversal of co-morbidities. The results were relatively short term for follow up. Further studies are necessary to confirm whether this is a long-term relationship.

Conclusions

The pre-operative NLR may be a predictive marker of weight loss and improving diabetes after SG.

Acronyms

neutrophil-lymphocyte ratio (NLR); laparoscopic sleeve gastrectomy (LSG); sleeve gastrectomy (SG); body weight (BW); Body Mass Index (BMI); type2 diabetes mellitus (T2DM); hypertension (HT); hyperlipidemia (HL); sleep apnea syndrome (SAS); percent excess weight loss (%EWL); percent total weight loss (%TWL); glucagon-like peptide 1 (GLP-1); metabolic syndrome (MS); hemoglobin A1c (HbA1c); farnesoid X receptor (FXR); duodenal-jejunal bypass (DJB); standard deviation (SD); post-operative one (POD1); prognostic nutritional index (PNI); complete remission (CR); partial remission (PR); improved (Improve); no change (NC); tight junction protein (claudin-1).

Declarations

The protocol for this research project was approved by a suitably constituted Ethics Committee of the Tokushima University Hospital (ToCMS:1277-4). Written informed consent was obtained from the patients for the publication. All data generated or analyzed during this study are included in this published article. Hideya Kashihara and the co-authors have no conflict of interest regarding this report. The authors of this study are grateful to the staff at the Department of Surgery, Tokushima University, for important contributions.

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Figures

Figure 1a

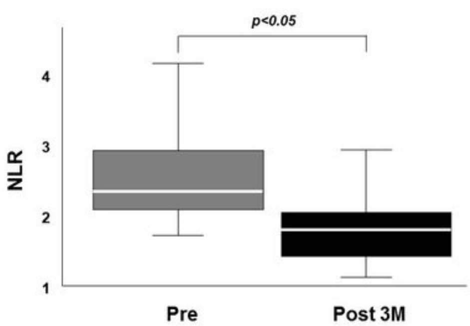

Figure 1b

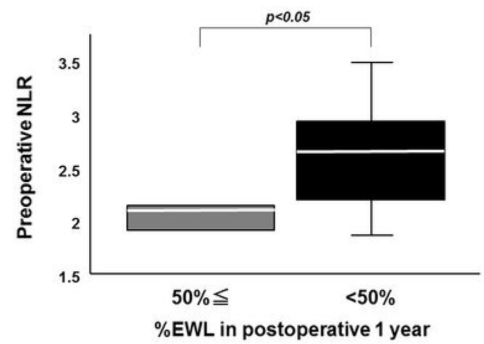

Figure 1c

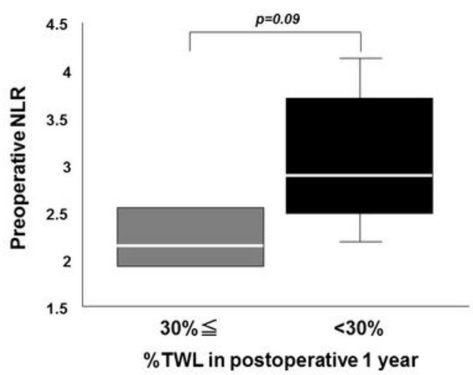

Figure 1d

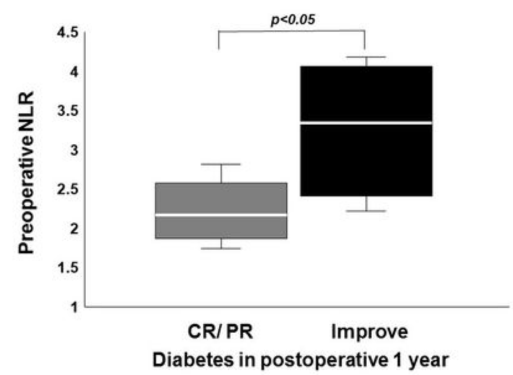

Figure 1

1a: The comparison between the pre-operative and three (3) months post-operative levels of the NLR. The values for each continuous variable were expressed as a mean ± the standard deviation (SD). The t-test was used for statistical analysis of the continuous variables. P<0.05 was interpreted as significant. 1b: The comparison of the levels of the pre-operative NLR between %EWL≥50% and <50% one (1) year post-operative. Values for each continuous variable were expressed as a mean ± the standard deviation (SD). The t-test was used for statistical analysis of the continuous variables. P<0.05 was interpreted as significant. 1c: The comparison of the levels of the pre-operative NLR between %TWL≥30% and <30% one (1) year post-operative. Values for each continuous variable were expressed as a mean ± the standard deviation (SD). The t-test was used for statistical analysis of the continuous variables. P<0.05 was interpreted as significant. 1d: The comparison of the levels of the pre-operative NLR between CR/ PR and Improve one (1) year post-operative. Values for each continuous variable were expressed as a mean ± the standard deviation (SD). The t-test was used for statistical analysis of the continuous variables. P<0.05 was interpreted as significant.