

Effect of Pancreas Omentoplasty and Sleeve Gastrectomy on Body Weight, Blood Sugar Levels, and Interleukin-6 in Diabetic and Obese Rats

Vicky Novitasari¹, Abdul Mughni¹, Nani Maharani³, K. Heri Nugroho^{2*}, Ignatius Riwanto¹

Department of Surgery, Faculty of Medicine, Diponegoro University, Indonesia¹

Department of Internal Medicine, Faculty of Medicine, Diponegoro University, Indonesia²

Department of Pharmacology, Faculty of Medicine, Diponegoro University, Indonesia³

Corresponding Author: 2*



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ABSTRACT

This study described the effectiveness of pancreas omentoplasty with sleeve gastrectomy on weight reduction, improving blood sugar levels and interleukin-6 in diabetic and obese rats. A randomized control group pretest-posttest study design was performed on 12 male Wistar rats aged 6 weeks induced with obesity and type 2 diabetes mellitus (DM) and grouped into sleeve gastrectomy (SG) group (P1) and SG group with pancreatic omentoplasty (P2). SG is done by partially removing the stomach in the major curvature and suturing it. Omentoplasty is performed by suturing the omentum to the pancreas. Body weight, fasting blood glucose levels, and interleukin-6 (IL-6) were examined before and 10 days after treatment. None of the rats experienced postoperative drop-out, and examination showed that they were obese with homogeneous body weight, blood glucose, and IL-6 levels. Data analysis showed body weight, blood glucose levels, and IL-6 after treatment were significantly decreased in both groups compared to levels before treatment. The improvement of these parameters was found to be significantly better in the group that received sleeve gastrectomy and pancreatic omentoplasty. In conclusion, sleeve gastrectomy with pancreatic omentoplasty significantly reduce body weight, blood sugar levels, and IL-6 better than sleeve gastrectomy procedure alone.



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1. Introduction

Diabetes Mellitus (DM) is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot use the insulin produced by the pancreas effectively [1], [2]. World Health Organization (WHO) data in 2014 showed that 8.5% of the world's population over 18 years old suffer from diabetes. Meanwhile, in Indonesia, the National's survey reported an increase in the prevalence of diabetes by 1.6% from 2013 to 2018. More than 95% of the population with diabetes have type 2 diabetes (T2D), 90% related to the incidence of obesity, which is called obesity-related type diabetes (O-T2D) [3], [4].

O-T2D can occur in chronically obese individuals with insulin disorders resulting in type 2 diabetes or in individuals with type 2 diabetes who experience side effects from oral therapy [5]. Obesity is a condition of excessive body fat with a rapidly increasing prevalence. Changes in lifestyle, genetic, maternal, environmental, aging, and drug side effects are some of the factors that can increase its incidence. The condition of low-grade systemic inflammation in obesity causes damage to the insulin receptor substrate (IRS), which will lead to insulin resistance. Inflammation in beta cells will cause acute pancreatitis, with the cytokine Interleukin 6 (IL-6) as the first predictor that can be detected [6], [7].

The increasing incidence of O-T2D with potential organ system damage encourages efforts to develop effective and adequate therapies. Metformin is currently the first-line therapy for diabetes, but studies have found it less effective in treating O-T2D. Thus, the treatment of O-T2D began to shift to operative treatment, with several studies showing the advantages of bariatric surgery in producing faster and more significant long-term improvements [8], [9].

Sleeve gastrectomy (SG) is a bariatric surgery technique that is simpler, easier for the operator to perform maneuvers and has a shorter duration than other techniques. SG is performed by removing nearly 80% of the stomach along the greater curvature, which will limit the amount of food intake and suppress the production of the hormone ghrelin to control hunger [10], [11]. The use of SG in the treatment of O-T2D has shown promising results, with a success rate of achieving complete remission of 60% within 5 years of observation. A modification of the SG using an omentoplasty procedure was developed to minimize the bleeding complications and leakage of the SG. By attaching the omentum to the perforated part, the presence of the activated omentum would trigger cell regeneration and tissue repair [12], [13]. Based on these facts, data, and previous research, an idea emerged to study the effectiveness of adding pancreatic omentoplasty procedures in SG surgery for O-T2D treatment. Pancreatic omentoplasty is expected to suppress pancreatic inflammation and increase insulin production, thereby increasing the complete remission rate in O-T2D patients.

2. MATERIALS AND METHODS

2.1 Animals and Treatment

An experimental study with a "Randomized Control Group Pretest-Posttest" design was carried out for 8 weeks at the Center for Food and Study Laboratory, Gadjah Mada University, Yogyakarta. Twelve male Wistar rats aged 6 weeks were used as experimental animal models. A high caloric and fat diet, consisting of 60% comfeed pars, 27.8% flour, 2% cholesterol, 0.2% cholic acid, 10% lard, and 2 ml/head/day fructose, was given to all rats for 4 weeks to achieve obesity. Intraperitoneal injection of streptozotocin in sodium citrate buffer pH 4.5 (single dose 60 mg/kg) was given for 3 days to induce a diabetic state. The Lee index > 300 was used to confirm obesity in experimental animals. After the adaptation period, all rats were randomly assigned to 2 groups: the group that received SG treatment (P1) and the group that received SG treatment and omentoplasty (P2). Blood sugar and IL-6 levels are measured before treatment.

2.2 Operation Procedure

After the rats had fasted for 10 hours, an intramuscular (IM) injection of ketamine (0.5 mg/kg) was given as an anesthetic. An incision was made at the abdomen until we reached the abdominal cavity. After identifying the stomach, a part of it is removed along the major curvature and then sutured. In the P2 group, the SG procedure was followed by omentoplasty by identifying and suturing the omentum to the pancreas. After the procedure is complete, suturing is done to close the wound. Postoperative care was carried out for 10 days by preventing hypothermia, changing the surgical wound dressing, and giving gentamycin ointment

every 3 days.

2.3 Evaluation

On the 10th postoperative day, body weight, fasting blood sugar (FBS), and IL-6 were measured. Examination of fasting blood sugar in plasma was carried out using the GOG-PAP (Glucose Oxidase-Peroxidase Aminoantypirin) method with a blood sugar kit. Expression of IL-6 levels was evaluated by enzyme-linked immunosorbent assay (ELISA).

2.4 Statistical Analysis

SPSS version 22 statistical analysis software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data analysis includes descriptive analysis and hypothesis testing. In descriptive analysis, the dependent variable is presented in the form of table mean, SD, median and box plot graph. Normality was tested by Shapiro–Wilk test. The Levene's test was used for the homogeneity test. To compare the results before and after the intervention, a paired t-test was performed, if the data was distributed normally or the non-parametric Wilcoxon test if not. An Independent t-test or Mann-Whitney analysis was performed to compare data from the two groups. The limit of the degree of significance is if $p \leq 0.05$ with a 95% confidence interval

3. RESULTS

All 12 rats recovered from anesthesia and surgical intervention well without any drop-out. Preliminary data consisting of body weight, GDP levels, and IL-6 were found to be normally distributed and homogeneous (Table 1).

Table 1. Descriptive, Normality, and Homogeneity Analysis of Rats' Characteristic

Group		Mean ± SD	Median (Min-Max)	Shapiro-Wilk	Levene's
Body weight (g/cm)					
Pre test	P1	249,60 ± 5,54	250,00 (241-258)	0,989*	0,976**
	P2	251,10 ± 5,30	250,50 (243-258)	0,481*	
Post test	P1	207,89 ± 5,28	207 (200 – 215)	0,748*	0,719**
	P2	194,50 ± 4,81	194 (189 – 201)	0,658*	
Delta	P1	-42,67 ± 1,00	-43 (-44 – (-41))	0,364*	0,017**
	P2	-56,33 ± 1,03	-56 (-58 – (-55))	0,473*	
Fasting blood sugar (mg/dl)					
Pre test	P1	265,82 ± 5,93	264,64 (256,07-274,48)	0,714*	0,498**
	P2	260,63 ± 5,39	261,08 (253,97-272,80)	0,118*	
Post test	P1	188,24 ± 5,76	187,45 (180,39 – 195,69)	0,353*	0,005
	P2	151,96 ± 17,17	146,86 (138,82 – 186,27)	0,005	
Delta	P1	-77,13 ± 1,14	-76,64 (-78,79 – (-75,68))	0,368*	0,000
	P2	-108,15 ± 15,56	-114,41 (-116,04 – (-76,49))	0,000	
Interleukin-6 (pg/ml)					
Pre test	P1	109,00 ± 4,77	109,20 (101,37-116,05)	0,695*	0,489**
	P2	108,22 ± 4,18	108,71 (101,37-115,07)	0,282*	
Post test	P1	100,39 ± 3,56	99,41 (95,50 – 107,24)	0,665*	0,556**
	P2	83,27 ± 3,95	84,74 (77,89 – 87,67)	0,204*	
Delta	P1	-9,46 ± 2,02	-9,79 (-11,74 – (-4,89))	0,064*	0,689**
	P2	-23,97 ± 1,20	-24,46 (-25,44 – (-22,50))	0,106*	

Description: *Normal ($p > 0,05$), **Homogen ($p > 0,05$).

Analysis of the body weight of experimental animals before and after treatment showed a normal distribution. The paired t-test found a significant difference in body weight before and after treatment in both groups, with group P2 showing greater weight loss than group P1. The unpaired t-test showed no

significant difference in body weight before treatment, and there was a significant difference in body weight after treatment and the difference. (Figure 1).

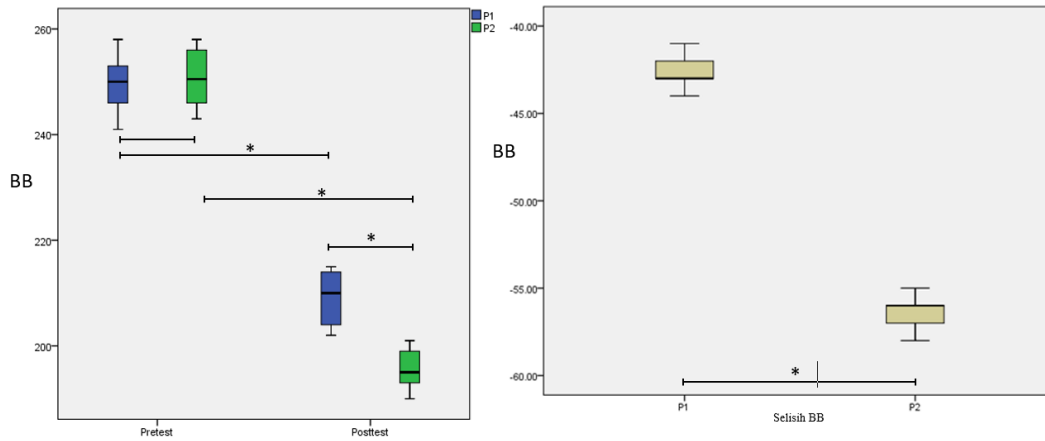


Figure 1 Boxplot graphs of the body weight changes from each group. P1: received sleeve gastrectomy treatment, P2: received sleeve gastrectomy and omentoplasty.

FBS level analysis before and after treatment showed an abnormal distribution. The paired t-test found significant differences in the levels of FBS before and after treatment in the two groups, with group P2 showing greater weight loss than group P1. The unpaired t-test showed no significant differences in the FBS level before treatment, and there were significant differences in the FBS level after treatment and the differences. (Figure 2).

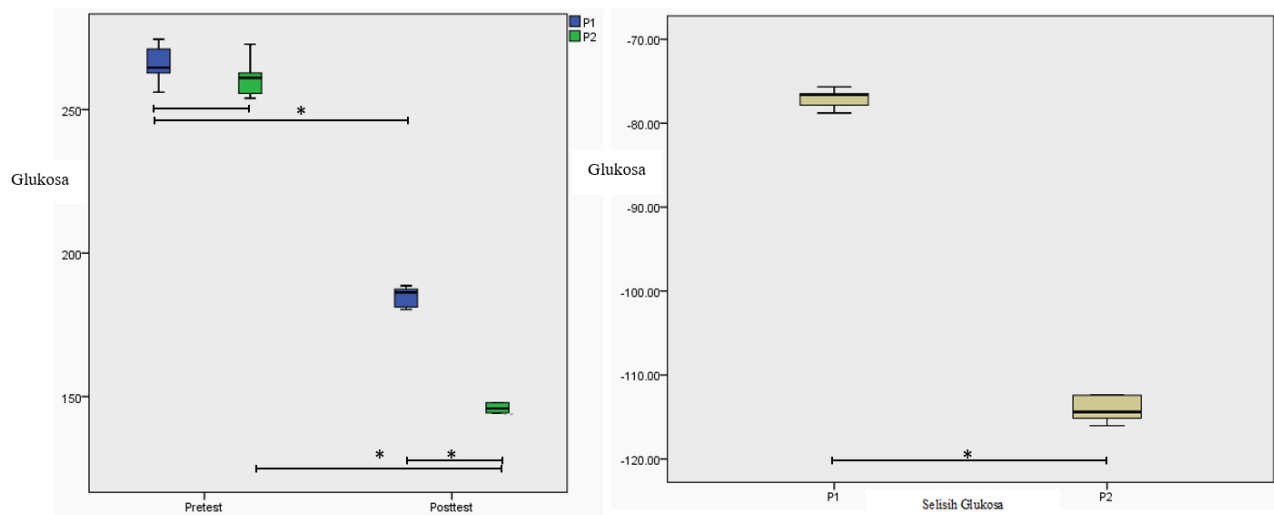


Figure 2 Boxplot graphs of the fasting blood sugar level changes from each group. P1: received sleeve gastrectomy treatment, P2: received sleeve gastrectomy and omentoplasty.

Analysis of IL-6 levels in experimental animals before and after treatment showed a normal distribution. The paired t-test showed a significant difference in IL-6 levels before and after treatment in the two groups, with the P2 group showing a greater decrease in IL-6 levels than the P1 group. Unpaired t-test showed no significant difference in IL-6 levels before treatment, and there were significant differences in IL-6 levels after treatment and the difference (Figure 3).

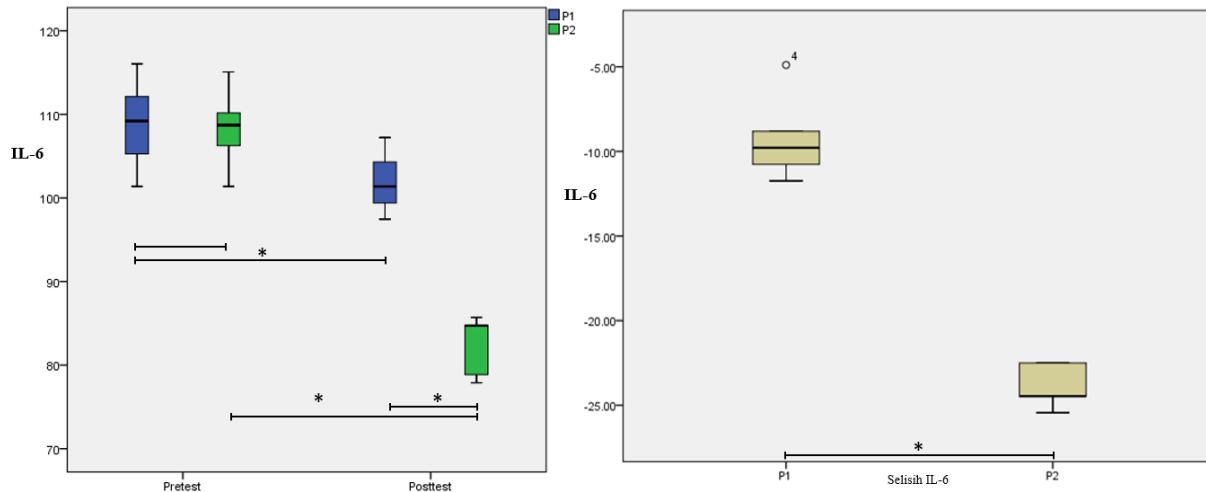


Figure 3 Boxplot graphs of the fasting blood sugar level changes from each group. P1: received sleeve gastrectomy treatment, P2: received sleeve gastrectomy and omentoplasty.

4. Discussion

This study aimed to see the effect of pancreatic omentoplasty on improving body weight, FBS, and IL-6 levels in obese rats with type II DM treated by SG. This study found that both groups experienced significant weight loss, with a greater amount of loss observed in the P2 group. [15] found similar results. They explained that the restriction mechanism of reducing gastric volume, decreasing ghrelin secretion, and increasing intestinal hormone secretion in the SG procedure could result in weight loss. In addition, the omentum is known to increase leptin secretion by reducing CRP and IL-6 levels, thereby indirectly reducing body weight [14].

The decrease in GDP levels found in both groups could be due to an increase in glucagon-like peptide-1 (GLP-1) levels, which will stimulate insulin release, driven by the incretin effect. In addition, GLP-1 also prevents beta-cell apoptosis, stimulates beta-cell development, and produces L-cells, so that insulin secretion into the blood will increase and lower blood sugar levels. Improvement in FBS levels in the P2 group is associated with pancreatic tissue regeneration through the effects of mesenchymal stem cells (MSCs) and myeloid-derived suppressor cells (MDS_c) in the omentum, which will increase insulin signaling activity in the pancreas [16], [17].

IL-6 levels were decreased in both groups after treatment, with the decrease in group P2 being greater than group P1. Improvement in IL-6 levels in the P2 group was associated with weight loss which could improve mitochondrial function in adipocytes and decrease cytokine production that plays an essential role in the control of inflammatory responses, vascular endothelial function, and immunity. Reduced adipocytokine secretion causes a decrease in the induction of pro-inflammatory cytokines such as IL-6, TNF α , and IL-1. This condition was found to be associated with a decrease in pro-inflammatory cytokines. This is consistent with the theory that omental stromal cells can reduce the level of pro-inflammatory cytokines such as IL-6, IL-1 and IL-12 [18], [19].

A study by [20] found that the SG procedure could improve body weight, glycemic status, and lipid profile, and increases serum adiponectin in mice with obese conditions and type 2 DM. In addition, [21] also reported that the SG procedure and pancreatic omentoplasty could reduce IL-1 levels and increase expression of pancreatic β -cells in rats with type II DM. Overall, the improvement in body weight, GDP,

and IL-6 levels was significantly better in animals that received SG and pancreatic omentoplasty

5. Conclusion

The SG procedure and pancreatic omentoplasty were found to significantly reduce body weight, GDP levels, and IL-6 levels compared to the SG procedure. Further research is needed to determine the effect of pancreatic omentoplasty and SG on other inflammatory cytokines implicated in obesity and the application of these procedures to human subjects to understand their direct effects.

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