R E S E A R C H   A R T I C L E

Combined Sleeve Gastrectomy and Omentoplasty Improves Inflammation and Insulin Resistance in Obese Rats with Type II Diabetes Mellitus: A Randomized Controlled Trials

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Abstract

BACKGROUND: Diabetes mellitus (DM) is often associated with obesity, which can lead to chronic inflammation. Sleeve gastrectomy (SG) is a common treatment for obesity. Combining SG with omentoplasty, might help reducing inflammation in pancreatic beta cells. However, there is limited research regarding the combined effects of SG and omentoplasty in type 2 DM (T2DM). This study was conducted to fill this gap by evaluating the impact on body weight, insulin resistance, glucagon expression, and levels of interleukins (IL)-1, IL-6, and IL-10 in obese rats with type II DM.

METHODS: An experimental study was conducted on 18 obese Wistar rats with DM that were randomized into: control, T1 (SG), and T2 (SG + omentoplasty). SG involved the surgical removal of a portion of the stomach to reduce its size, while omentoplasty utilized the omentum to target inflammation in pancreatic beta cells. Venous blood samples were taken from subjects one day before and ten days after the intervention to measure the biomedical parameters with various methods. Data was statistically analyzed using paired t-tests for pre-test and post-test differences, and Post Hoc tests or Mann-Whitney tests for hypothesis testing.

RESULTS: All rats were confirmed to have obesity and DM according to the Lee index and blood glucose levels. T2 group exhibited a significant decrease in body weight, homeostatic model assessment of insulin resistance (HOMA-IR) values were lower, and glucagon expression, IL-1, IL-6, and IL-10 levels were significantly greater compared to both control and T1 groups.

CONCLUSION: The combination of SG and omentoplasty significantly improves inflammation and insulin resistance in obese rats with T2DM.

KEYWORDS: diabetes mellitus, sleeve gastrectomy, omentoplasty, inflammation, obesity

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to insufficient insulin production by the pancreas or ineffective use of the insulin produced by the pancreas.(1,2) In 2021, the worldwide prevalence of diabetes among individuals aged 20 to 79 was estimated at 10.5%, or 536.6 million people. This figure is expected to increase to 12.2%, or 783.2 million people, by 2045.(3) Indonesia rank sixth among countries with the highest number of DM patients and estimated to increase to

16.7 million patients per year by 2045.(4,5) Obesity is one of the major risk factors for DM and has become a significant health challenge.(6,7) Obesity triggers continuous inflammatory mechanisms due to the accumulation of excess fat in adipose tissues and organs, which can lead to insulin resistance.(6-8) With the increasing incidence of obesity and type 2 DM (T2DM) globally and its impact on other bodily systems, therapeutic efforts are continuously being developed.(9,10)

Non-surgical approaches to managing obesity and diabetes often fall short due to poor compliance, highlighting the need for more effective interventions.(11,12) The emergence of bariatric surgery has represented a pivotal breakthrough in addressing these conditions, offering promising outcomes.(11,12) Studies have demonstrated that bariatric surgery not only yields better metabolic parameters but also facilitates diabetes remission, underscoring its potential as a transformative treatment option for individuals struggling with obesity and diabetes.(11,12)

Sleeve gastrectomy (SG) is one of the most popular technique of bariatric surgery performed by cutting off nearly 80% of the stomach from the pylorus along the greater curvature to the gastric fundus.(13) Five years after undergoing SG, a significant proportion of patients experienced positive outcomes, including the resolution or improvement of DM as well as enhancements in arterial hypertension and dyslipidemia.(14) Overall, the findings suggest that SG leads to substantial and long-lasting weight loss and notable improvements in associated health conditions.(14) The success rate of this procedure is believed to be improvable by addressing inflammation in pancreatic beta cells, thus requiring additional interventions or modifications to enhance this success rate.(15-17)

Omentoplasty, a surgical intervention, involves affixing the omentum to particular organs. The omentum serves as an organ pivotal in inflammation regulation, promoting revascularization, and tissue rejuvenation. Additionally, omental adipose tissue contributes to localized immunological responses and harbors a multitude of multipotent mesenchymal stem cells (MSCs), which aid in tissue regeneration. Consequently, omentoplasty targeted at the pancreas holds potential to improve pancreatic function by to suppressing the inflammatory process and increase insulin production, thus enhancing the complete remission rate in T2DM patients.(18) However, there is limited research on the combined effects of SG and omentoplasty in T2DM subjects. Therefore, this study was conducted to evaluate the combined effects of SG and omentoplasty in experimental obese rats with T2DM. Body weight, fasting blood sugar, homeostatic model assessment of insulin resistance (HOMA-IR) values, glucagon expression, interleukin (IL)-1, IL-6, and IL-10 levels were used in this study as predictors to assess the effects of omentoplasty related to the inflammatory process and insulin resistance.

Methods

Research Design and Animal Induction
Eighteen male Wistar rats, aged 8 weeks, were obtained and housed at the Central Laboratory for Food Studies, Universitas Gadjah Mada, Yogyakarta. All rats were fed a high-calorie and high-fat diet for 4 weeks to induce obesity, characterized by a Lee index >300.(19) Streptozotocin injections (Sigma Aldrich-Merck, St. Louis, MO, USA) were administered intraperitoneally in sodium citrate buffer pH 4.5 at a single dose of 45 mg/kgBW to induce DM. Blood samples were taken from the infraorbital vein of the rats for blood glucose examination, with blood glucose levels ≥200 mg/dL considered indicative of DM status.(20) Prior to the commencement of the study, the study protocol was approved by the Independent Ethics Committee of Universitas Diponegoro/Dr. Kariadi Hospital Semarang (No. 118/ EC/H/FK-UNDIP/XII/2020).

Experimental Design
A randomized control group pretest-posttest design was employed in this study. Once DM and obesity statuses were confirmed, all rats were randomized into three groups: control (C) as the positive control, SG treatment (T1), and SG treatment with omentoplasty (T2). Body weight, HOMA-IR values, IL-1, IL-6, and IL-10 levels were examined before the intervention and 10 days after intervention using blood samples taken from the infraorbital vein of the rats (Figure 1). Between day-1 and day-10, the rats were given normal diet. Glucagon expression was examined as a post-test-only value. HOMA-IR values were calculated using a nonlinear mathematical model between fasting insulin and fasting glucose levels.(21)

SG Procedure
Rats were anesthetized with an intramuscular injection of 20 mg/kgBW ketamine. A subcostal oblique incision was made on the left side of the abdomen to access the abdominal cavity. Saline solution was injected into the stomach to enlarge the volume and facilitate the SG procedure. The stomach was incised just above the greater curvature line until only 50% of the volume remained. The incised portion
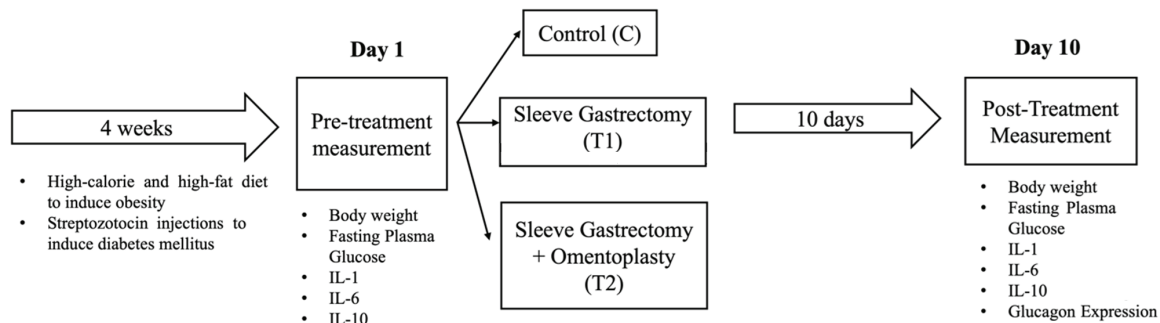
Figure 1. The timeline of the study of the three studied groups.

was clamped to minimize bleeding before excision. The remaining stomach was sutured with polyglycolic acid (PGA) 5.0 thread (Figure 2A).

Omentoplasty Procedure

The omentum from the rat's abdomen was harvested, and the pancreas was identified. The omentum was attached and sutured to the pancreas, then closed with simple sutures using PGA 5.0 thread. The abdominal incision was closed layer by layer with PGA 3.0 thread (Figure 2B).

Measurements of IL-1, IL-10, IL-6 Levels

Venous blood samples were collected from the rats on two separate occasions: before treatment (day-1) and 10 days after treatment (day-10). The IL-1, IL-10, and IL-6 were quantified using the enzyme-linked immunosorbent assay (ELISA) method with Rat IL-1 beta ELISA Kit (Cat. No. RK00009; Abclonal, Woburn, MA, USA), Rat IL-10 FAST ELISA Kit (Cat. No. RK04846; Abclonal), and Mouse IL-6 ELISA Kit (Cat. No. KE10007; Proteintech, Manchester, UK), respectively. The blood samples were processed according to the manufacturer's instructions, which involved adding the samples to wells coated with specific antibodies, incubating to allow binding, adding detection antibodies and substrate solutions, and measuring absorbance using a microplate reader.

Measurement of Fasting Glucose and Fasting Insulin Levels

Venous blood samples were collected after an overnight fast on day-1 and day-10 for the measurement of fasting glucose and fasting insulin level. Fasting glucose level were measured using (GOG-PAP) method using a standard glucose assay kit from Sigma-Aldrich (St. Louis, MO, USA), following the kit's instructions. The processed involved adding the blood samples to test strips or assay plates, processing them as per the protocol,

and reading the glucose levels using a glucometer or microplate reader. Meanwhile, the fasting insulin level were measured using ELISA method using Rat INS (Insulin) ELISA Kit (Cat. No. E-EL-R3034; Elabscience, Houston, TX, USA).

Calculation of HOMA-IR

After the measurement of fasting insulin and fasting glucose, the HOMA-IR was calculated with the following formula: (Fasting insulin, uIU/mL)*(Fasting glucose, mg/dL)/405. (22) The mentioned formula for HOMA-IR was based on a study on human, however the use in Wistar rats of it has been validated by previous study.(23)

Measurement of Glucagon Level

Venous blood samples were collected ten days after the intervention, and plasma was separated for analysis of glucagon level Glucagon level were measured using Rat GC (Glucagon) ELISA Kit (Cat. No. E-EL-R0425; Elabscience). The assay involved adding plasma samples to a microplate coated with a glucagon-specific antibody, followed by a secondary antibody linked to an enzyme. After adding a substrate solution, a color change occurred, and the absorbance was measured using a microplate reader to determine glucagon concentrations. These concentrations were then statistically analyzed to compare pre- and post-intervention levels within each group and between control, T1 and T2 groups.

Statistical Analysis

Body weight, HOMA-IR values, glucagon expression, IL-1, IL-6, and IL-10 levels were presented descriptively as means and standard deviations (SD) for each group. Paired t-tests were used to compare pre-test and post-test data. One-way ANOVA and Post Hoc tests or Kruskal-Wallis and Mann-Whitney tests were used to test hypotheses. A p-value<0.05 was considered significant.
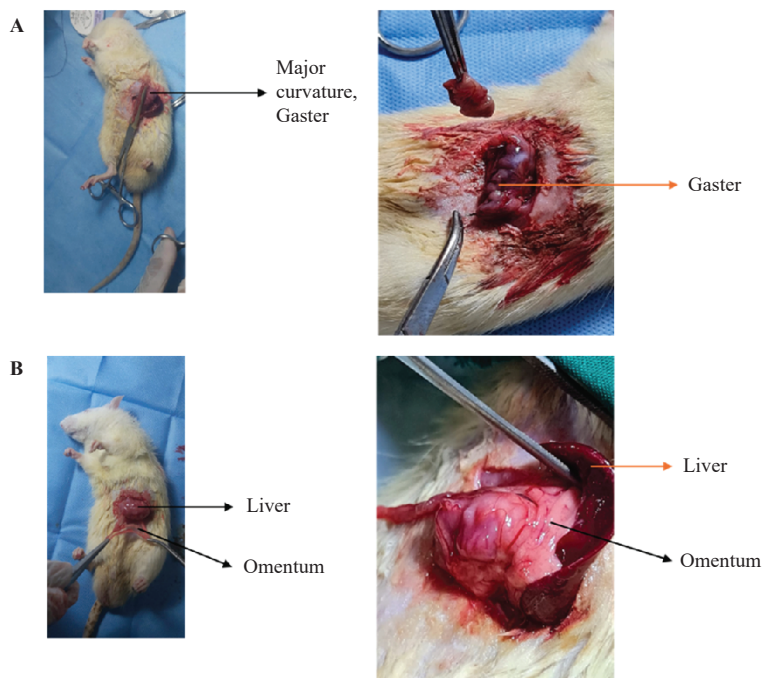
Figure 2. SG and omentoplasty procedures. A: For the SG procedure, the sample underwent a medial abdominal incision, layer by layer, until the abdominal cavity was visible. Exploration was performed to locate the stomach. The greater curvature was identified, and an SG was performed on the greater curvature. The wound was then sutured layer by layer. B: For the omentoplasty procedure, the sample underwent a medial abdominal incision, layer by layer, until the abdominal cavity was visible. After performing the sleeve gastrectomy, exploration was carried out to locate the greater omentum, which was then excised. The excised greater omentum was attached to the head of the pancreas through suturing.

Results

Clinical Characteristic of Samples

All 18 rats were confirmed to have DM and obesity upon completion of the induction period. During the intervention, no rats died until the 10th day post-intervention. Basic characteristics of the research samples showed that the mean Lee index in all three groups was nearly similar and consistently >300 g/cm. The mean Lee Index for the control group was 322.94±6.54 g/cm, for T1 group was 325.44±5.69 g/cm, while for T2 group was 325.84 ± 5.92 g/cm. Similarly, fasting glucose levels yielded similar results, confirming the DM condition in all rats before surgical intervention (Table 1).

SG and Omentoplasty Induced Greatest Weight Loss

Analysis of the changes in body weight from the samples indicates that all three groups experienced a significant decrease in weight post-procedure. T2 group exhibited the greatest weight reduction from 256.50±5.25 g to 194.50±4.80 g compared to the control and T1 groups (Table 1). One-Way ANOVA and LSD Post Hoc tests showed significant differences in post-test data among each group of control, T1, and T2 groups. T2 group showed the greatest weight loss compared to control and T1 groups (Supplementary 1).

SG and Omentoplasty Decreased HOMA-IR

HOMA-IR levels increased significantly in the control group (from 38.54±0.34 to 121.66±4.07) and T1 group

(from 39.67±0.83 to 59.51±2.79), while T2 group showed a slight but significant decrease (from 38.24±0.21 to 34.34±2.09) (Table 1). One-Way ANOVA and Post Hoc analysis revealed significant differences between T2 group *vs.* control group ($p<0.001$) as well as T2 group vs T1 group ($p<0.001$) (Supplementary 2).

Glucagon Expression was the Highest in SG and Omentoplasty Group

Measurement of glucagon expression was only conducted once after the intervention was administered. The glucagon expression analysis revealed significant differences in glucagon levels among the control group and the two treatment groups after the interventions. The control group exhibited very low glucagon expression with a mean value of 1.42±.63 pg/mL, reflecting the untreated state of the diabetic rats. In T1 group, glucagon expression was significantly higher with a mean value of 18.22±.34 pg/mL. This suggested that SG surgery impacts glucagon production or regulation, possibly due to changes in the digestive system and metabolic processes following the procedure. In T2 group, subjects showed the highest glucagon expression with a mean value of 37.05±.48 pg/mL (Table 2).

SG and Omentoplasty Decreased IL-1, IL-6, IL-10

Analysis of IL-1 levels showed a significant difference between pre-test and post-test levels among groups T2 and T1 groups. In the control group, there was no significant difference in pre-test levels compared to post-test levels (Table 1). Hypothesis testing indicated significant

Table 1. Body weight, fasting plasma glucose, HOMA-IR, IL-1, IL-6, IL-10 levels before and after treatment.

Parameters	Group	Pre-treatment	Post-treatment	*p*-value	Delta Changes
Body weight	Control	252.90±6.57	241.40±6.75	<0.001*	-11.500±3.85
	T1	254.90±5.44	207. 80±5.27	<0.001*	-47.10±3.54
	T2	256.50±5.25	194.50±4.80	<0.001*	-62.0 ±2.90
Fasting plasma glucose	Control	266.61±5.16	267.30±3.2	0.836	3.78±0.71
	T1	265.81±5.93	188.25±5.5	<0.001*	-76.77±1.13
	T2	264.35±5.95	151.71±17.1	<0.001*	-108.06±15.51
HOMA-IR	Control	38.54±0.34	121.66±4.07	<0.001*	83.12±4.35
	T1	39.67±0.83	59.51±2.79	<0.001*	19.83±2.39
	T2	38.24±0.21	34.34±2.09	0.028*	-3.90±2.08
IL-1	Control	91.38±3.61	91.27±4.06	0.897	-0.11±2.22
	T1	89.98±3.12	73.67±3.81	<0.001*	-16.31±2.01
	T2	88.90±2.73	60.20±2.84	<0.001*	-28.70 ±1.61
IL-6	Control	110.18±3.81	114.91±4.26	<0.001*	4.73±0.96
	T1	109.00±4.77	100.39±3.56	<0.001*	-23.97±1.20
	T2	108.22±4.18	83.27±3.95	<0.001*	-9.46±2.02
IL-10	Control	113.73±3.49	80.30±2.97	<0.001*	-33.43±1.20
	T1	116.51±1.07	27.68±1.90	<0.001*	-88.84±1.46
	T2	116.93±0.68	12.82±1.09	<0.001*	-104.11±1.43

*p<0.05 indicating significant difference between pre-treatment and post-treatmemt data, analyzed with paired t-test.

differences between each group. T2 group demonstrated better improvement in IL-1 levels compared to the control and T1 groups (Supplementary 3).

Paired t-test results comparing the changes in IL-6 levels between pre-test and post-test showed significant differences in both treatment groups (Table 1). T2 group exhibited a greater decrease in IL-6 levels compared to pre-treatment, with a difference of -23.97±1.20 pg/mL. Unpaired t-test between grops results showed no significant differences in pre-test IL-6 levels, while post-test data and delta changes in IL-6 levels showed to be significantly different.

The paired t-test results comparing changes in IL-10 levels between pre-test and post-test showed significant differences in all three groups (Table 1). T2 group significantly had the lowest IL-10 levels compared to the

control group and T1. One-Way ANOVA and Post Hoc analysis revealed significant differences in post-treatment between groups (Supplementary 4).

Discussion

This study evaluated the effects of combining SG and omentoplasty on obesity and DM, revealing that this combination significantly reduced body weight compared to SG alone and the control group. Eventhough SG alone already able to reduced body weight, however incorporating omentoplasty may further contribute to weight reduction. SG decreases obesity-related inflammation, and the results of this study is align with prior research indicating that SG effectively reduces body weight by restricting gastric volume, lowering ghrelin secretion, and boosting the secretion of intestinal hormones like glucagon like peptide 1 (GLP-1) and peptide YY (PYY).(24,25)

Our study demonstrated that both SG and SG with omentoplasty significantly lowered fasting glucose levels and HOMA-IR compared to the control group, indicating that these surgical interventions effectively enhance glycemic control in diabetic rats. In the control group, there was a significant increase in HOMA-IR levels after

Table 2. Glucagon expression analysis.

Group	Glucagon Expression (Mean±SD)	*p*-value
Control	1.42±2.63	<0.000*
T1	18.22±0.34	
T2	37.05±0.48	

*p<0.05 indicating significant difference between all groups, analyzed with One-Way ANOVA.

10 days post-treatment, even though this group did not undergo any surgical intervention. This increase could be attributed to the natural progression of diabetes in obese rats, which tends to exacerbate insulin resistance over time without any therapeutic intervention. The absence of any treatment likely allowed the disease to progress unchecked, resulting in higher HOMA-IR levels. In contrast, the T2 group, which received both SG and omentoplasty, exhibited a slight but significant decrease in HOMA-IR levels. This suggests that the combined procedure not only halted the progression of insulin resistance but also slightly improved it. The omentoplasty component, which leverages the unique physiology of the omentum, may contribute a protective effect against insulin resistance.(18) The omentum is known for its immunological and metabolic functions, which might help in reducing inflammation in pancreatic beta cells and improving insulin sensitivity.(26) Thus, the findings indicate that the addition of omentoplasty to SG could enhance the overall effectiveness of the treatment in managing insulin resistance in obese diabetic rats.

Although postprandial glucose levels were not measured, which would have offered additional insights into the treatments' effects on overall blood glucose regulation, these findings are promising. They suggest that SG and omentoplasty could be a valuable approach in addressing diabetes and lay the groundwork for future research.

Analysis of glucagon expression indicates higher levels in the group receiving both SG and omentoplasty, while the control group shows lower averages. This suggests an increase in glucagon expression after intervention compared to the control. Glucagon, produced by pancreatic alpha cells when blood sugar drops, implies that the SG and omentoplasty interventions result in a more significant reduction in blood sugar compared to SG alone.

Patients with T2DM often have high fasting plasma glucagon levels and cannot suppress its secretion after meals.(27) Historically, treatments like somatostatin and glucagon receptor (GCGR) antagonists have shown benefits in controlling hyperglycemia, but they come with side effects such as increased hepatic transaminases and low-density lipoprotein (LDL) cholesterol. Interestingly, glucagon stimulates insulin release via GLP-1 receptor (GLP-1R) in beta cells, leading to the exploration of glucagon/GLP-1 dual co-agonists for their superior effects on glucose and lipid metabolism. These co-agonists have progressed to clinical trials, showing promise primarily in treating obesity.(27,28) Elevated glucagon-to-insulin ratios have been observed in diabetic Goto-Kakizaki rats following SG, and an early rise in serum glucagon levels has been noted in patients.(27)

Furthermore, based on another study on rats, SG was found to expand the alpha-cell population at the expense of beta-cells, contributing to increased glucagon response without affecting plasma glucose levels.(29)

Obesity's surplus adipose tissue influences metabolism by releasing hormones, glycerol, and various substances like leptin, cytokines, adiponectin, and pro-inflammatory agents, as well as by liberating Non-esterified fatty acids (NEFA). The rise in HOMA-IR levels among the control group indicates insulin resistance induced by obesity and DM. Nonetheless, interventions such as SG and the combination of SG with omentoplasty demonstrate a decline in HOMA-IR values. SG diminishes gastric volume, resulting in minimal malabsorption effects, quicker gastric emptying, and heightened intestinal motility. Furthermore, excising the gastric fundus lowers ghrelin hormone levels, predominantly synthesized in this region. Ghrelin plays a pivotal role in curbing appetite, impacting weight reduction and fostering enhancements in glucose metabolism and insulin levels.(30)

In this study, levels of IL-1 and IL-6 were markedly reduced in both treatment groups compared to the control group, with the SG and omentoplasty combination group showing the most pronounced effect. The enhancements observed in IL-1 and IL-6 levels within this group can be linked to weight loss, resulting in elevated adiponectin hormone levels and reduced secretion of adipocytokines. A decline in the secretion of adipocytokines results in a reduction in the triggering of inflammatory cytokines like IL-6, tumor necrosis factor (TNF)-α, and IL-1.(25,26) This aligns with prior studies suggesting that stromal cells from the omentum can diminish the presence of pro-inflammatory cytokines like IL-1, IL-6, and IL-12.(27) In addition, a study found that SG increases serum adiponectin levels, improves glycemic control, and enhances lipid profiles in obese rats with T2DM.(28) Another research indicated that SG combined with pancreatic omentoplasty significantly reduces IL-1 levels and increases pancreatic β cell expression in rats with T2DM.(29)

The decrease in IL-10 levels found in all three groups is consistent with previous studies stating that levels of anti-inflammatory cytokines, including IL-10, decrease in morbidly obese patients with sleep apnea.(31) IL-10 is known to inhibit inflammation by increasing immune responses during inflammatory events.(31) The level of adipose tissue impacts the levels of adipokines like adiponectin and leptin, as well as inflammatory cytokines such as C-reactive protein (CRP), IL-6, IL-10, and TNF-α in the plasma.(32) Furthermore, in individuals with obesity,

there is an inverse correlation between IL-10 and both body mass index and fasting glucose levels.(32) Previous studies have found that IL-10 also correlates negatively with insulin produced by the pancreas in obese subjects.(33)

Most of the parameters in this study were only measured twice, which was 1 day before and 10 days after the intervention, which may not capture potential effects emerging beyond that timeframe. Thus, further investigations are warranted to evaluate its impacts over a more diverse duration. Moreover, the assessment of glycemic control in this study relied on glucagon expression and HOMA-IR values, prompting the possibility of developing additional parameters to better characterize the effects of SG and omentoplasty on patient glycemic management.

Conclusion

In conclusion, the study demonstrated that SG combined with omentoplasty significantly improved metabolic parameters in obese Wistar rats with DM. The combined treatment led to substantial reductions in body weight, insulin resistance, and fasting glucose levels, along with decreased levels of IL-1, IL-6 and IL-10. Additionally, glucagon expression was better regulated in the SG and omentoplasty combination group compared to the control and SG only groups. These findings suggest that the addition of omentoplasty to SG could enhance the therapeutic effects of bariatric surgery by addressing inflammation and improving metabolic outcomes in diabetic obesity.

Acknowledgments

Authors Contribution

HN and AM were involved in planning and supervised the work. IKAP, ATP, and VN performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and designed the figures, performed the calculations and statistical analysis. HN and AM aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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