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Association between sleeve gastrectomy and TGF-β and IL-10 expression in obesity and diabetes mellitus rats

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ABSTRACT

Background:
The world's prevalence of diabetes mellitus (DM) is about 422 million cases. Obesity can increase the likelihood of various diseases and conditions associated with increased mortality, including type 2 diabetes mellitus. One of obesity surgery treatments that is currently used is the sleeve gastrectomy (SG). Sleeve gastrectomy is the most effective and significant long-term therapy for weight loss and preventing various comorbidities such as heart disease. Meanwhile, the Transfroming growth factor-β (TGF-β) and Interleukin-10 (IL-10) are anti-inflammatory cytokines that play role mostly on the process of atherosclerosis in obesity and diabetes mellitus subjects.
Objective: This study aimed to analyze the effect of SG on the expression of TGF-β and IL-10 in obesity and diabetes mellitus animal models.
Methods: We conducted *in vivo* experimental study with post-test control group design on 15 male rats (Sprague Dawley) that was randomly divided into 3 groups: K1 (negative control), K2 (positive control with obesity and DM) and P1 (obese and DM rats treated with SG). Obesity and DM were induced by giving high calorie and fat diet for 8 weeks and 40 mg/kg body weight (BW) streptozotocin (STZ) and 120 ml/kgBW of nicotinamide intraperitoneally for 5 days. After the 10th day of SG procedure, we analyzed the body weight, fasting blood glucose, and gene expression of TGF-β and IL-10 using the PCR method.
Results: There was significant increase of TGF-β (p = 0,005) and IL-10 (p = 0,002) gene expression in P1 compared to K1 and K2. There was a significant decrease in body weight and fasting blood sugar levels (p=0,000) in the P1 compared to the K2.
Conclusion: Sleeve gastectomy improved the expression of atherosclerosis anti-inflammatory cytokines (TGF-β and IL-10) in abdominal aorta. In addition, SG also decreased body weight and fasting blood sugar levels of obese and DM rats.

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1. Introduction

Diabetes mellitus is one of non-infectious metabollic disease with inadequate control of blood levels of glucose caused by destruction of beta cells in the pancreas or insensitivity of insulin. About 422 million people have diabetes in the world, mostly coming from low- and middle-income countries with 1.5 million deaths directly attributed to diabetes each year. Over time, diabetes could lead into serious damage to the heart, blood vessels, eyes, kidneys and nerves.[1] Obesity is also a risk factor for atherosclerosis, which can increase the likelihood of various diseases and conditions associated with increased mortality, such as type 2 diabetes mellitus (DM), cardiovascular disease (CVD) and metabolic syndrome (MetS), chronic kidney disease, hyperlipidemia, hypertension, nonalcoholic fatty liver disease, osteoarthritis, and depression.[2] According to the World Health Organization (WHO), in 2022 about 890 million people or 43% of the world's adult population were obese. In low-income and middle-income countries, overweight and obesity rates are increasing, especially in urban areas. Treating obesity with weight loss through lifestyle changes is often accompanied by inconsistencies and emotional difficulties.[3]

One of the obesity managements that is currently developed and most frequently used is bariatric surgery with sleeve gastrectomy technique. This procedure removes

most of the stomach with the aim of influencing the patient's appetite regulation. In addition, this procedure can increase Glucagon Like Peptide (GLP-1), adiponectin and decrease ghrelin due to removal of the fundus and corpus of the gaster. According to data from the American Society for Metabolic & Bariatric Surgery, when it comes to bariatric procedures, SG is now the most popular procedure, being utilized 59.4% of the time. This procedure gives good results in the form of weight loss rate up to 60% of excess body weight within 6 months after procedure. In addition, the remission rate of type II diabetes reaches 92%. This makes SG the most effective and significant long-term therapy for weight loss and preventing various comorbidities such as type II DM and heart disease.[3]

One of the long-term cardiac complications of having both obesity and diabetes mellitus is atherosclerosis. Atherosclerosis is a cardiovascular disease that becomes the biggest problem for developed and developing countries. It is predicted that 23.6 million people globally in 2030 will die due to cardiovascular disease with atherosclerosis is the cause major mortality. The main principles of preventing atherosclerosis are maintaining blood pressure, maintaining body biochemistry and adequate physical activity.[4] Atherosclerosis is an inflammatory process mediated by several inflammatory mediators, namely cytokines and chemokines. When in an inflammatory state, the immune system responds by inducing inflammatory cytokines in the form of pro-inflammatory cytokines and anti-inflammatory cytokines. Interleukin-10 is an anti-inflammatory cytokine that works by strengthening the immune system (immunostimulator) and suppressing inflammatory conditions or excessive immune system reactions (immunosuppressant) from the action of pro-inflammatory cytokines. The IL-10 response is generated from the humoral immune system of T cells and cellular B cells. Transforming growth factor-β is a multifunctional cytokine with pleiotropic properties that exerts different effects on cell proliferation and differentiation. Thus, it can be concluded that one of anti-inflammatory mediators that play an important role in the atherosclerosis process are TGF-β and IL-10.[5] This research analyzed the effect of SG in body weight, fasting blood glucose levels, and the expression of anti-inflammatory cytokines of atherosclerosis, such as TGF-β and IL-10, that were taken from abdominal aorta of obesity and DM-induced Sprague Dawley rat models.

2. Methods

Research design

This research is an experimental *in vivo* design with posts test control group design. The independent variable of this research is the SG procedure, and the dependent variables are TGF-β and IL-10 gene expression. All rats were randomly divided into three groups: K1 group (negative control) consists of healthy rats without obesity and DM induction, K2 group (positive control) consists of obesity and DM induced rats, and P1 group consists of obesity and DM induced rats who received sleeve gastrectomy treatment 10 days before termination.

Research sample and size

Sprague Dawley rats aged 4-6 weeks, with body weight around 150 – 200 grams and male sex were selected as the inclusion criteria of rats. While exclusion criteria of this study were rats that have disabilities, were not active, sick, and had contraindications to the SG procedure. All rats used in the study were obtained from the iRATco animal rat provider.

In determining the sample size needed for each treatment group, the resource equation method was used. The formula was: E = (n x R) – R with "E" value must be between 10 and 20. If E is less than 10 then adding more samples will increase the chance of getting more significant results, but if it is more than 20 then the sample size is considered sufficient. “n” value was minimum sample size per group and “R” value was number of experimental groups. In experimental research, to anticipate the loss of experimental units, a correction is made with 1/(1-f), where f is the proportion of experimental units that are lost or withdraw or drop out.[6] So based on these calculations, 5 samples are needed per each group so that the minimum number of samples is 15 rats.

Time and location of research

The research and data collection were carried out from July-August 2022, and the research location for obesity and DM induction, SG operation process, and treatment of rats was at the Central Laboratory of Food and Study Gajah Mada University Yogyakarta. Polymerase chain reaction was conducted at the Stem Cell and Cancer Research (SCCR) Laboratory of Sultan Agung Islamic University.

Experimental animals’ treatment and induction

All 15 male Sprague Dawley rats that met the inclusion and exclusion criteria were housed at room temperature with access to drinking water and given a high-calorie, high-fat diet for 8 weeks before surgery for obesity induction. High fat diet contains 8% corn oil, 44% sweetened condensed milk, and 48% purine rat food. K1 group was given standard diet as healthy control group, K2 as positive control group and P1 group was given a high calorie and fat diet for 8 weeks to achieve obesity and the atherosclerosis process. To induce diabetes condition, K2 and P1 groups were injected intraperitoneally with STZ at a dose of 40 mg/kg BW in citrate buffer (pH 4.5) and 120 ml/kg bodyweight of nicotinamide in phosphate-buffered saline in the last five days of the 8th week. After STZ induction, rats in the K2 and P1 groups were fasted for 4–6 hours to be carried out for fasting blood glucose (FBG) measurement, taken from the tail vein/lateral veil of rats. This measurement was done 5 days after STZ injection and before termination using a GlucoDR Bio-sensor glucometer. Rats are declared diabetic if FBG is >126 mg/dL.

Sleeve gastrectomy procedure and post-surgery treatment

After 8 weeks of acclimatization and induction, rats were fasted for 10 hours, then ketamine intraperitoneal injection was carried out at a dose of 2 mg/kg body weight. Antisepsis

and asepsis were done on the surgical area. A midline supra-umbilical incision was performed, deepening layer by layer. The body of the stomach occupies 50% of its volume above the greater curvature. Gaster was then identified, all gastric corpus was cut. The abdominal cavity was cleaned with warm 0.9% NaCl and the surgical area was then stitched with polypropylene 5.0 layer by layer (Figure 1). After SG procedure, P1 group was continued to be given HFD.

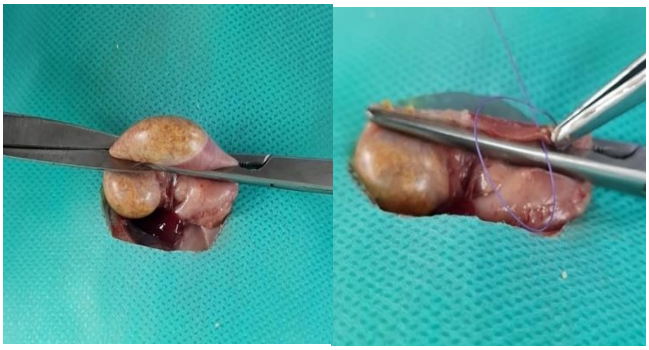

Figure 1. Sleeve gastrectomy procedure in rats; FR: Forestomach, LR: Limiting Ridge

Aorta sampling and PCR procedure

Ten days after SG procedure, all rats were terminated with cloroform. Rats were dissected from the chest to the abdomen, then the aorta was taken out. The aorta was fixed in Bouin's solution, then the sample was brought into the laboratory for PCR examination. Before termination the body weight and FBG glucose levels were measured.

The process of ribonucleic acid (RNA) extraction involves several steps, including sample preparation, separation phase, RNA precipitation, and PCR. A sample was prepared by placing the suspension in a conical tube, Trizol (TRI) reagent was added, and the sample was separated into 5 parts. The sample was then incubated for 2-15 minutes, and the RNA is precipitated using aqueous phase, ethanol, and TRI Reagent. The RNA pellet was then resuspended with 0.5% sodium dodecylsulphate (SDS) solution or diethylpyrocarbonate (DEPC) water. The RNA concentration was determined by adding 1X Tris-EDTA (TE) buffer, a high standard calibration solution, and a low standard calibration solution. The RNA standard was then added to a 0.5 ml tube PCR tube, and the RNA sample was mixed with the standard. The complementary DNA (cDNA) synthesis was performed by adding the reagent to a microcentrifuge tube, resuspensing the tube with a spinner, and incubating the tube with a thermal cycler at 70°C for 10 minutes. The RNA sample was then ready for analysis or dissolution at -20°C. Analysis of the results was performed by measuring (Cq/Ct) compared with standard, non-template control, and positive control.

Data analysis

Data cleaning, coding, and tabulation are done after the data was gathered. Analyzing data also involved testing hypotheses and descriptive analysis. Data on the body weight, fasting blood glucose, TGF-β, and IL-10 gene expression were reported in terms of mean and standard deviation. The Shapiro-Wilk test was used to perform the normality test and the Levene test was used to perform the homogeneity test. In the data that is normally distributed and homogeneous, a comparative analysis between groups was performed using the parametric ANOVA test and then the LSD post hoc test. Meanwhile, for data that were not normally distributed and not homogeneous, a comparative analysis between groups was performed using the Kruskal-Wallis non-parametric test and then the LSD post hoc test. Data analysis was performed using SPSS version 26.0 for Windows.

3. Result

Baseline characteristic

All research animals went through acclimatization, randomization and treatment according to the research flow from start to finish. There were no experimental animals that dropped out during treatment. Sample characteristics on body weight and fasting blood glucose levels are shown in Table 1. The average body weight decreased in the K2 and P1 groups. The FBG levels did not change significantly in the K1 and K2 groups. Meanwhile, in the P1 group, there was a significant decrease in FBG levels. Then all groups of mice were terminated, and PCR examination of the abdominal aorta was performed to see the expression of TGF-β and IL-10 genes.

Table 1. Levels of fasting blood glucose and body weight of research samples

Day	Parameter	K1 (n = 5)	K2 (n = 5)	P1 (n = 5)
1	BW (grams)	166.60 ± 4.03	172.60 ± 3.05	169.60 ± 3.20
56	BW (grams)	221.60 ± 4.39	265.80 ± 3.49	266.60 ± 3.49
	FBG (mg/dl)	68.00 ± 1.58	270.20 ± 6.83	265.40 ± 4.15
66	BW (grams)	231.80 ± 4.32	264.60 ± 3.28	232.00 ± 5.33
	FBG (mg/dl)	68.60 ± 2.07	271.00 ± 6.89	114.40 ± 3.20

Description: BW: Body Weight; FBG: Fasting Blood Glucose; K1: Negative control group (healthy/normal mice without induction without treatment); K2: Positive control group (obese and DM induced mice without SG treatment); P1: The treatment group (obese induced mice and DM was performed SG)

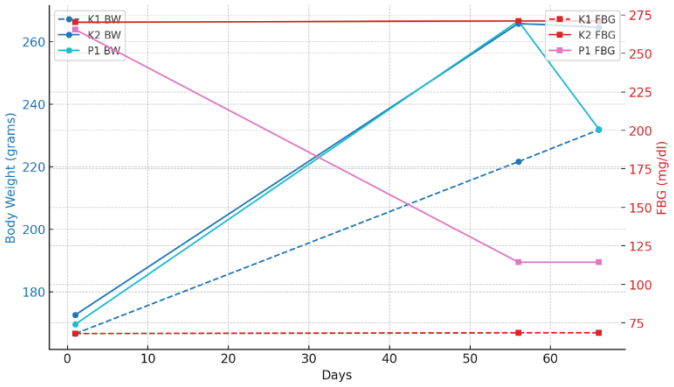

Figure 2. Levels of fasting blood glucose and body weight of research samples

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Body weight

Right before termination date, group K2 showed the highest body weight (264.60 ± 3.28 grams) compared with group P1 (232.00 ± 5.33 grams) and group K1 (231.80 ± 4.32 grams). Data from all groups showed a normal and homogeneous distribution (p > 0.05), then continued with the Anova test. The results of the Anova test showed a significant difference in body weight in K1, K2, and P1 groups (p = 0.000, 0.000, 0.000). The LSD post-study trial showed that SG significantly reduced body weight in P1 group (p <0.05) compared with K2 as positive control group.

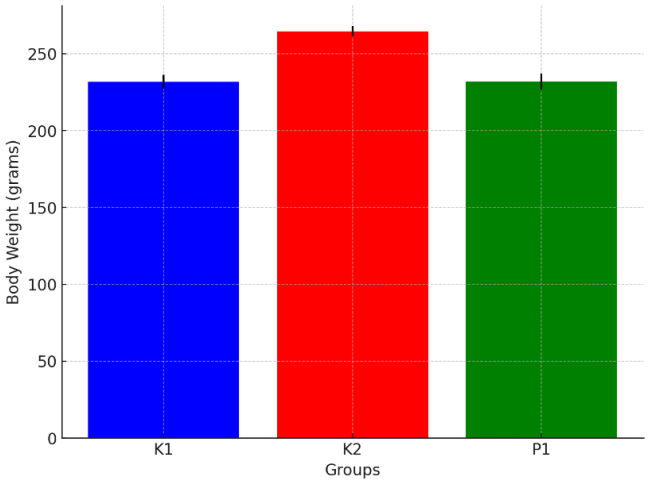

Figure 3. Body Weight Comparison Right Before Termination.

Fasting blood glucose

Group K2 showed the highest FBG (264.60 ± 3.28) compared to the P1 (114.40 ± 3.20) and K1 (68.60 ± 2.07). The results of the Anova test showed that there were significant (p=0.000) differences in FBG in all groups. The LSD post-hoc test showed that SG significantly reduced FBG in obese and DM rats (p <0.05) compared with K1 and K2 groups as negative and positive control group

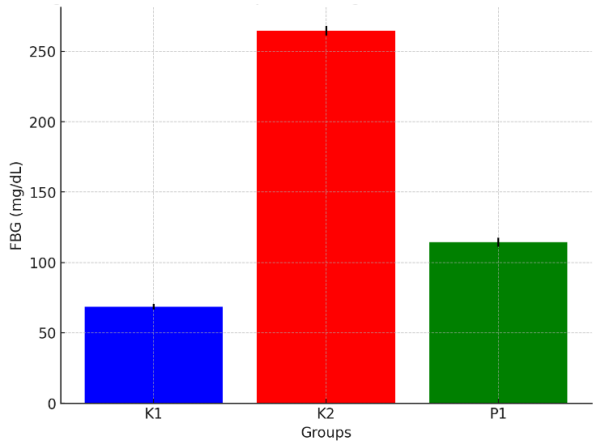

Figure 4. Fasting Blood Glucose Comparison Right Before Termination.

TGF-β expression

The relative mRNA expression of the TGF-β gene in rat abdominal aorta tissue samples was measured using the qRT-PCR method and calculated using the Livak method to obtain Relative quantification (Rq) values. The Rq value data was analyzed by the Saphiro-Wilk normality test and continued with Kruskal-Wallis non-parametric test to determine the differences between treatment groups. Table 3 shows the results of the Kruskal Wallis TGF-β test. From the results of the post hoc test (Table 2), it was found that there was a significant difference in the expression of TGF-β between the P1 group and the K1 and the K2 group (p = 0.000). The group of obese and diabetic rats that underwent SG (P1) was found to express higher TGF-β compared to the obese and DM group that did not undergo sleeve gastrectomy (K2) and the healthy group of rats (K1).

IL-10 expression

The relative mRNA expression of the IL-10 gene in rat abdominal aorta tissue samples was measured using the qRT-PCR method and calculated using the Livak method to obtain Relative quantification (Rq) values. The Rq value data was analyzed by the Saphiro-Wilk normality test and continued with Kruskal-Wallis non-parametric test to determine the differences between treatment groups. Table 3 showed the mean expression of IL-10 in the abdominal aorta of Sprague Dawley rats in groups K1, K2 and P1 along with the normality test results. From post-hoc LSD test (Table 2), it was found that there was a significant difference in the expression of IL-10 between the P1 group and the K1 group (p = 0.048) and the K2 group (p = 0.049). The group of obese and DM rats that underwent SG (P1) was found to express higher IL-10 compared to the Obese and DM group that did not undergo SG (K2) and the healthy group (K1).

Table 2. The least significant difference (LSD) post hoc test results

Group I	Group II	p-values
TGF-β mRNA expression		
K1	K2	0.821
K1	P1	0.000*
K2	P1	0.000*
IL-10 mRNA expression		
K1	K2	0.989
K1	P1	0.048*
K2	P1	0.049*
Body weight		
K1	K2	0.000*
K1	P1	0.944
K2	P1	0.000*
Fasting Blood Glucose levels		
K1	K2	0.000*
	P1	0.000*
K2	P1	0.000*

*significant (p< 0.05); BW: Body Weight; FBG: Fasting Blood Glucose; TGF-β: Transfroming growth factor-β; IL-10: interleukin-10; mRNA: messenger Ribonucleic acid; K1: Negative control group (healthy/normal mice without induction without treatment); K2: Positive control group (obese and DM induced mice without SG treatment); P1: The treatment group (obese induced mice and DM was performed SG)

Table 3. The result of Kruskal Walis TGF-β and IL-10 test

Group	Median (min – max)	p-values
TGF-β mRNA expression		
K1	1.050 (1.05 – 1.06)	0.005*
K2	1.726 (0.90 – 2.15)	
P1	25.53 (15.66– 33.07)	
IL-10 mRNA expression		
K1	1.05 (1.05 – 1.06)	0.002*
K2	7.36 (2.92 – 8.00)	
P1	352.14 (129.79 – 2,352.53)	

*significant; TGF-β: Transfroming growth factor-β; IL-10: Interleukin-10; mRNA: messenger Ribonucleid acid; K1: Negative control group (healthy/normal mice without induction without treatment); K2: Positive control group (obese and DM induced mice without SG treatment); P1: The treatment group (obese induced mice and DM was performed SG)

4. Discussion

This study aimed to analyze the effect of SG on the expression of anti-inflammatory cytokines TGF-β and IL-10 in the abdominal aorta on the process of atherosclerosis in obese and DM rats. Of all the rats that underwent SG, it was found that there was an improvement in both BW and FBG in rats. The average weight loss in rats was 29.44 grams, which was around 9-12% of initial body weight before treatment. The decrease in FBG in rats was obtained by an average of 151.49 mg/dl. These results are supported by a number of meta-analyses which have revealed that SG surgery results in relatively large short-term weight loss (± 41 kg in 30 days) and provides about 77% improvement in DM patients.[7] For long-term effects, a meta-analysis of RCTs with 2 years of follow-up showed that bariatric surgery resulted in weight loss (± 26 kg) and DM remission. Another study revealed that SG can improve control of CVD risk factors with remission rates of 73% in DM, 63% in hypertension, and 65% in hyperlipidemia.[8] The result of this study showed that SG procedure could be considered to be done on diabetes mellitus and obese patients as it indicates to lower body weight and fasting blood glucose, which benefits patient's overall prognosis.

In this study, there was a significant increase in the expression of TGF-β (25.620 ± 3.032) in the P1 group who underwent SG treatment compared with a group of healthy mice (1.052 ± 0.002) and a group of positive control mice (1.626 ± 0.203). This is in line with a previous study by Brethauer et al who examined the effect of gastric bypass on inflammatory mediators where there was an increase in anti-inflammatory mediators in obese patients undergoing gastric bypass.[9]

An insignificant increase occurred in the K2 group to K1. According to research Jiang et.al showed that changes in TGF-β activity locally in tissues are important in the process of atherogenesis. Increased TGF-β expression was also found in obese individuals. This is because the function of TGF-β in inhibiting the pro-inflammatory cytokine IL-6 is increased in obese individuals.[6] Seay et al. reported that the increased expression of TGF-β was thought to function to repair damaged arterial vascular structures, especially in new cells and matrix structures in the tunica intima with transdifferentiation of vascular smooth muscle cells (VSMCs).[7] The protective function of TGF-β also activates tissue apoptotic mechanisms, so that the growth to the tunica intima is not excessive. In atheroma-filled conditions, TGF-β functions to prevent proliferation and further migration of smooth muscle cells and endothelial cells so that the formation of atheroma plaques can be prevented.[10,11] It was found that TGF-β stimulates the production of extracellular matrix and the expression of adhesion molecules involved in leukocyte recruitment. Moreover, has various direct effects on immune cells, including inhibition of foam cell formation in macrophages. Taken together, these in vitro activities are consistent with the hypothesis that TGF-β plays a role in the maintenance of normal vascular wall architecture.[10,12]

A significant increase was found in the group undergoing SG due to the response of SG which decreased adipose tissue in the body. Along with the decrease in adipose there is an increase in 50-adenosine monophosphate-activated protein kinase or AMPK, which is a metabolic sensor that regulates homeostasis.[13] In several studies, AMPK levels were found to increase after SG procedures.[14] In addition, SG also regulates inflammation through a central pathway in hypothalamus, which is triggered by hyperphagia and metabolic dysregulation. With the decrease in adipose tissue in the body, hormonal mechanisms change in these tissues. The most abundant immune cells in adipose tissue are macrophages. Where macrophages in adipose cells have 2 phenotypes, namely M1 (pro-inflammatory) and M2 (anti-inflammatory). With the decrease in adipose tissue, macrophage cells will switch to the dominance of the M2 phenotype. The M2 macrophages together with Th2 and T-cell regulators will produce anti-inflammatory cytokines including TGF-β, IL-10, IL-5 and Interferon-γ.[15]

The result of this study showed that sleeve gastrectomy procedure had potential benefit on increasing TGF-β levels, which had protective function on influencing immune regulation to produce anti-inflammatory cytokines. This positive finding could give better clinical impact on obese and diabetes mellitus patients. However, further research is needed to verify this effect.

In this study, there was an increase in IL-10 expression in the K2 group (Obese and DM) against P1 (SG). This is because in K2 rats with obesity and diabetes, there is also an increase in proinflammatory cytokines circulating in the blood and tissues. Its natural mechanism to reduce this process is to release anti-inflammatory cytokines, in this case the main ones are IL-10 and TGF-β.[16,17]

There was a significant increase in IL-10 expression in the P1 group compared to K1 and K2. These results are also consistent with the theory that IL-10 which can be found in atherosclerotic lesions plays a potent protective role by inhibiting Th1 responses, promoting the proliferation and differentiation of regulatory T cells.[18] Also, previous studies have shown that IL-10 modulates several possible cellular pathways, plays an important role in the development and stability of atherosclerosis, including NF-kB activation, tissue factor and cyclooxygenase-2 expression.[19,20]

The recovery rate from DM in SG procedure is 92%. In this study it was also proven that there was an improvement in FBG levels in rats treated with SG. This repair mechanism is triggered by a decrease in the hormone ghrelin and an increase in CGK (Cyclic Guanosine Monophosphate Binding Protein Kinase) as neuropeptide that stimulates insulin secretion, GIP (Gastric Inhibitory Polypeptide), GLP1 and GLP2 which play a key role in improving metabolic control in the body. Along with the improvement of insulin sensitivity in post SG individuals, it also plays a role in the anti-inflammatory properties of insulin repair through several mechanisms. According to a study by Ditri and Joseph, insulin plays a role in the anti-inflammatory process through the suppression of NFkB, Intercellular Adhesion Molecule-1 (ICAM-1) and Monocyte Chemoattractant Protein-1 (MCP-1) on aortic endothelial cells. In addition, insulin sensitization also suppresses the transcription of the pro-inflammatory factors AP- 1 (Activator Protein 1) and EGR-1 (Early Growth Response Factor 1). These transcription factors regulate the genes for matrix metalloproteinase (MMP), pro-thrombotic tissue factor (TF) and Plasminogen Activator Inhibitor-1 (PAI-1) as anti-fibrinolytic.[22]

This research showed the effect of sleeve gastrectomy on IL-10, that sleeve gastrectomy could increase anti-inflammatory mediators which play role in the process of repair and remodeling of blood vessels in individuals with obesity and diabetes who experience atherosclerosis, thereby preventing the development of atherosclerosis into cardiovascular disease. Although this study showed potential benefits from SG procedure on obese and diabetes mellitus rats' model, there are still limitations. In this study, we specifically performed tests on young male rats, recognizing that both obesity and diabetes mellitus (DM) affect individuals of both sexes and are more prevalent with increasing age. The decision to use young male rats was based on the need to control for potential hormonal variations and minimize sex-related differences that could influence the outcomes. While the metabolic and inflammatory pathways involved in obesity and DM are consistent across sexes, future studies should aim to include both male and female subjects, as well as older animals, to better reflect the broader population affected by these conditions. This study also did not include histopathological examination of the blood vessels in study samples. It would be better if future research could examine the histopathology of blood vessels so that we could see the atherosclerosis process microscopically. Apart from that, further research with data on humans who have undergone sleeve gastrectomy is also needed to see the anti-inflammatory response to atherosclerosis that occurs in humans. This would provide a more comprehensive understanding of how SG influences body weight, glucose metabolism, and inflammatory cytokine expression across different demographic groups.

5. Conclusion

Based on the results of this study it can be concluded that sleeve gastrectomy performed on obese and DM rats can reduce body weight, fasting blood glucose levels and increased expression of atherosclerosis anti-inflammatory cytokines (TGF-β and IL-10) in abdominal aorta. From this conclusion, it is hoped that this research brings new insight, becomes a basis for reference for further research as well as treatment of obesity and DM against the occurrence of atherosclerosis using the sleeve gastrectomy procedure.

Ethical Approval

Ethical clearance was obtained from The Health Research Ethics Commission, Faculty of Medicine, Diponegoro University to all procedures involving experimental animals. The number of ethical approval is no. 58/EC/H/FK-Undip/VII/2022.

Conflicts of Interest

There is no conflict of interest in the process of making this article.

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Author Contributions

All authors contributed to this work. SNM, SAP, MAS, AMR, YWP were involved in concepting and planning the research, SNM performed the data acquisition/collection, calculated the experimental data and performed the analysis, and drafted the manuscript. SAP, MAS, AMR, and YWP supervised all research processes. The final manuscript was read and approved by all authors.

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List of Abbreviations

AP-1: Activator Protein 1, CGK: Cyclic Guanosine Monophosphate Binding Protein Kinase, DM: Diabetes Mellitus, DMT-II: Diabetes Mellitus tipe II, DNA: Deoxyribonucleic Acid, EGR-1: Early Growth Response Factor 1, GIP: Gastric Inhibitory Polypeptide, GLP-1: Glukagon-Like Peptide-1, ICAM-1: Intercellular Adhesion Molecule-1, IL: Interleukin, MetS: Metabolic Syndromes, MCP-1: Monocyte Chemoattractant Protein-1, NF-kB: Nuclear Factor-kappa B, PAI-1: Plasminogen Activator Inhibitor-1, Rq: Relative quantification, SG: Sleeve gastrectomy, STZ: Streptozotocin, TGF-β: Transforming Growth Factor Beta, TNF-α: Tumor Necrosis Factor-alpha, VSMCs: Vascular Smooth Muscle Cells, WHO: World Health Organization

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