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Sleeve gastrectomy and pancreas omentoplasty improved β cell insulin expression and interleukin-1β serum level in non-obese diabetes mellitus rat

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ABSTRACT

Background: Diabetes mellitus is one of the health problems that is growing rapidly today. In Asia, majority of the population are non-obese with Type 2 Diabetes Mellitus (T2DM). Two main defects of T2DM, insulin resistance and impaired insulin secretion due to reduced pancreatic β cells. Persistent metabolic stress due to hyperglycemic conditions, causes inflammation of the islets of Langerhans. Interleukin-1β (IL-1β) signaling is the most frequent pathway inducing β cell dysfunction. The bariatric Sleeve Gastrectomy (SG) procedure increases particular hormone which stimulates β cell growth and pancreatic insulin production. Aside from the role as a blood glucose regulator, insulin also plays a role in anti-inflammatory modulation. Omentoplasty can be used to wrap organ or tissue structures. The Omentum has unique biological functions, including promote tissue regeneration and anti-inflammatory effect. The study evaluates the effect of Sleeve Gastrectomy and pancreas Omentoplasty procedures on β cell insulin expression and Interleukin-1β (IL-1β) serum levels in non-obese diabetes mellitus subjects.

Methods: Experimental study with "post-test control group design" on 27 rats with Diabetes Mellitus was divided into 3 groups: K (control), P1 (Sleeve Gastrectomy), P2 (Sleeve Gastrectomy + Omentoplasty). 10 days after procedure, we evaluated the insulin expression of β cells using monoclonal antibody anti-insulin stain and IL-1β serum levels using rat IL-1β Enzyme-Linked Immunosorbent Assay (ELISA) kit. Statistical analysis with Kruskal Wallis and Mann Whitney test. Correlation test with Spearman.

Results: β cell insulin expression increased in P2 ($p=0.020$), compared to control. While the IL-1β serum levels reduced significantly in all groups ($p<0.001$) compared to control. Moderate negative correlation ($r = -0.476$) between β cell insulin expression and IL-1β serum levels.

Conclusion: Sleeve gastrectomy and omentoplasty increased β cell insulin expression and decreased IL-1 β serum levels in non-obese rats with diabetes mellitus.

Keywords: diabetes mellitus, insulin, IL-1β, omentoplasty, sleeve gastrectomy.
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INTRODUCTION

Diabetes Mellitus is one of the fastest-growing health problems of the 21st century. International Diabetes Federation (IDF) data for 2019 show that 463 million people currently live with diabetes, with Indonesia ranked 6th in the world.[1,2]

Diabetes mellitus type 2 (T2DM) is the most common type of diabetes (90% of cases). Obesity being considered as a major factor in the pathogenesis of T2DM.[3] However, in Asian countries, the majority body mass index population was in non-obese category. China and Japan show that more than 60% of T2DM patients were non-obese. The data also stated that non-obese T2DM patients have a higher mortality rate than obese T2DM.[4-6]

The two main defects of non-obese T2DM are impaired pancreatic insulin secretion and insulin resistance.[4] Impaired insulin secretion occurs because reduced mass of pancreatic β cells that produce insulin.[7] Persistent metabolic stress due to hyperglycemia conditions activates the body's inflammatory defense mechanism. In the pancreas, it causes inflammation of the islets of Langerhans, which results in the release of local cytokines. These can activate NF-κB which contributes to β cell dysfunction and apoptosis.[8] Interleukin-1β (IL-1β) signaling pathway is the most common and high-impact cytokines in activating β cell dysfunction in several T2DM research models. Among the factors that stimulate islet macrophages to secrete IL-1β in vivo in human islands are amyloid polypeptides, free fatty acids (FFA), and endocannabinoids. Maedler et al. demonstrated that hyperglycemia can induce IL-1β production by stimulating pro-apoptotic FFA receptors on β cells.[9]

Insulin not only reduces the adverse effects of hyperglycemia through its metabolic regulation, but also directly modulates inflammatory mediators and acts on immune cells to enhance immunocompetent abilities. In other words, insulin acts as anti-inflammatory regulator. Increased pancreatic insulin secretion can suppress the inflammatory process in the body which in turn will improve insulin resistance.[10]

Current management of T2DM focuses a lot on the prevention and management of complications, not on the full remission, because they considered T2DM as an irreversible, chronic, and progressive disease. On the other hand, surgical therapy is starting to attract researchers' interest as therapy in T2DM to improve patient's glucose status by reducing the need for insulin. Bariatric surgery, in obese patients, results in full diabetes resolution in over 90% patients. The underlying mechanisms are thought due to significant weight loss and calorie restriction. However, a large-scale study with 608 patients and a 14-year follow-up indicated that diabetes resolution occurred even before significant weight loss appears.[11]

Sleeve Gastrectomy (SG) is the most popular bariatric procedure used today.[12,13] SG has a fairly good outcome in obese patients. However, its effectiveness in curing non-obese T2DM patients is questionable. Several metabolic changes occurred after this procedure, including increased glucagon-like peptide-1 (GLP-1) levels, which stimulates growth and inhibits apoptosis of pancreatic β cells.[12,14] GLP-1 also has function as anti-inflammatory modulator in local tissue.[15]

Omentoplasty procedures are often used to cover/fill defects, or wrap organ/tissue structures. Omentoplasty has been used in a variety of surgical procedures.[16] Omentum has unique biological functions, including neovascularization, anti-inflammatory, and tissue regeneration. The "activated omentum" contains several groups of function: cells that can suppress Th17; cells which rich source for growth factors; mesenchymal stem cell type.[17] Omentoplasty of the pancreas is expected to reduce inflammation and induce regeneration of Langerhans β cells.

There has not been any research linking the combination of SG and pancreas Omentoplasty procedure effects on pancreas histology and systemic pro-inflammatory cytokine serum levels in non-obese T2DM subjects. This study will evaluate the β-cell insulin expression and Interleukin-1β (IL-1β) serum levels in non-obese T2DM subjects underwent Sleeve Gastrectomy and pancreatic Omentoplasty and analyzed correlation between them.

MATERIALS AND METHODS

Animals

Twenty-seven male Sprague-Dawley rats, 6-8 weeks old, 170-200 grams weight, were obtained and treated in the Integrated Research and Testing Laboratory (LPPT), Gadjah Mada University, Yogyakarta. All were adapted for 1 week to laboratory conditions before the study begun. Standard diet applied.

Induction materials

Rats were injected with 230 mg/kg Nicotinamide (NA) intraperitoneally 15 minutes before single-dose intraperitoneal administration of 65 mg/kg Streptozotocin (STZ).[18] On the 3rd day after induction, We took blood sample from infraorbital venous of non-fasting rats. The glucose serum level was measured. Glucose level ≥ 200 mg/dl categorized as Diabetes Mellitus.[19]

Sleeve gastrectomy

These procedures carried out after rats were sedated using intramuscular injection of ketamine hydrochloride 20 mg/kg body weight. The abdominal cavity was opened with an oblique left subcostal incision. the stomach was injected with saline solution to expand the volume to make it easier to measure and cut above the mayor curvature line until its remain only 50% of its volume. To minimize the bleeding, we clamp the line before excision. Then we closed sewn the residual stomach with PGA 5.0 thread running suture (Figure 1).

Pancreas omentoplasty

Pancreas rat identified as mini tapering lump that lies between duodenum and spleen. Histologically, β cells were found dominantly in the tail of pancreas rat, adhere to the spleen. So we aim to cover the tail of pancreas with pedicled-omentum, and closed the wrap using only one loose simple suture PGA 5.0, to avoid blood vessel injury of the spleen. Closure of abdominal incision using whole layer simple suture PGA 3.0.

Experimental design

After diabetes mellitus was confirmed, rats were divided into 3 groups randomly. Control (group K), Sleeve Gastrectomy procedure (group P1), Sleeve Gastrectomy and pancreas Omentoplasty (group P2). Bodyweight, glucose serum level, and IL-1β serum level were measured one day before surgery, 5th day and 10th-day post-procedure. Glucose serum levels were obtained with Glucose GOD FS (DiaSys) kit. IL-1β serum level measured using rat IL-1β Enzyme-Linked Immunosorbent Assay (ELISA) kit.

At 10th day, Rats were terminated and the pancreas extracted. Paraffin blocks were made and analyze in Anatomical Pathology Laboratory of the Faculty of Medicine, Sebelas Maret University, Surakarta. Each sample was cut about 4 microns thickness and stained with Immunohistochemistry (IHC) monoclonal antibody anti-Insulin. β cell insulin expression was measured by intensity percentage of all brown stained cells in islet Langerhans from a significant area with 400x microscopic magnification view in 5 different field views within one block paraffin. All samples were confirmed by 2 pathologists.

Statistical analysis

Bodyweight, glucose serum level, β cell insulin expression, and IL-1β serum level were presented descriptively in the form of mean, SD, and number of sample tables for each group. β cell insulin expression, and IL-1β serum level at 10th-day post-procedure data were tested for normality, followed by One Way ANOVA for for IL-1β serum level, non-parametric test Kruskal Wallis for β cell insulin expression followed with Mann Whitney. Correlation between β cell insulin expression and IL-1β serum level using Spearman test. Limit $p \leq 0.05$ significance level with 95% confidence intervals. Data were analyzed with SPSS software 15.0 for Windows.

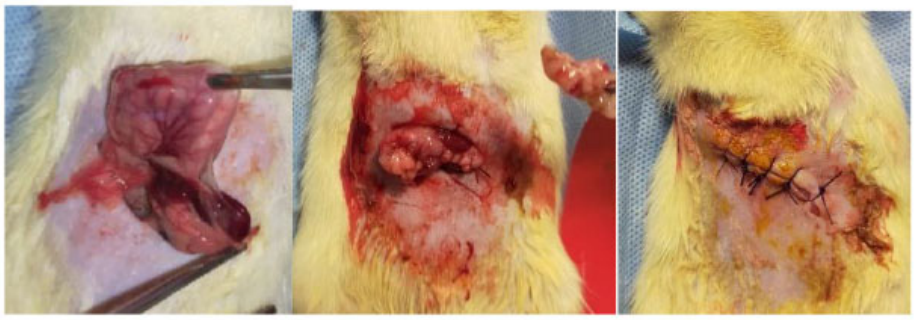

Figure 1. Sleeve Gastrectomy Procedure. Left to right: stomach identification; partial stomach removal and closed-sutured; abdominal left subcostal oblique incision closure.

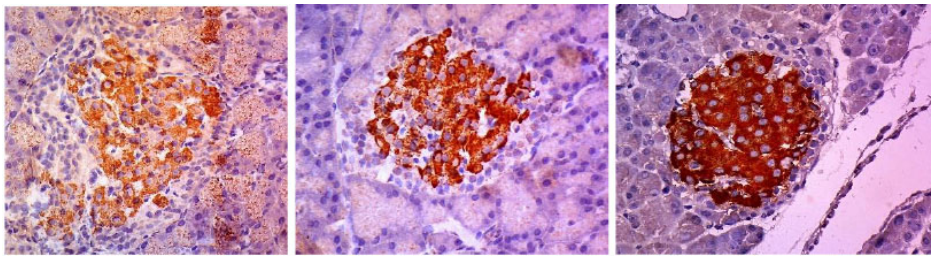

Figure 2. β cell insulin expression using IHC monoclonal antibody anti-insulin. Left to right : Control group; SG-only group; SG + Omentoplasty group (different brown staining intensity).

Table 1. Body weight descriptive data (gram)

Day	Group	N	Mean ± SD	Median
D-1	K	6	177.17 ± 5.64	176.5
	P1	8	173.63 ± 3.38	174
	P2	8	173.88 ± 4.26	175
5th	K	6	160.67 ± 4.50	159.5
	P1	8	156.88 ± 3.23	157
	P2	8	157.50 ± 4.04	158
10th	K	6	144.17 ± 6.34	143
	P1	8	139.38 ± 3.58	140.5
	P2	8	142.75 ± 5.28	142.5

Table 2. Glucose serum level descriptive data (mg/dL)

Day	Group	N	Mean ± SD	Median
D-1	K	6	266.54 ± 3.99	264.59
	P1	8	265.47 ± 3.79	264.98
	P2	8	265.40 ± 5.79	264.79
5th	K	6	271.48 ± 2.27	271.49
	P1	8	193.66 ± 11.65	191.90
	P2	8	179.07 ± 4.78	180.33
10th	K	6	274.76 ± 2.81	274.32
	P1	8	174.44 ± 6.97	177.65
	P2	8	158.87 ± 5.03	

RESULTS

All 27 rats were confirmed to have diabetes mellitus on the third day after induction. On the process after having (or not) Sleeve Gastrectomy and/or Omentoplasty procedure, five rats died. Three rats in the control group, one rat in SG-only group, and one rat in SG + Omentoplasty group. The remaining 22 rats which still alive until the 10th day after procedure were being analyzed.

Baseline Characteristic

Sample characteristics on body weight and glucose serum level were presented in table 1 and table 2. Mean body weight was almost similar between all groups on the same measured day. Decreasing body weight was observed on 5th day and 10th day post-procedure, with 10th day bodyweight being the lightest (Table 1). Mean glucose serum levels were similar in all groups on 1-Day pre-procedure. as time passed, glucose serum level observed clearly different results between all groups. P2 (SG + Omentoplasty) group have the most improved mean glucose serum level than the rest, at 10th day post-procedure (158.87 ± 5.03) (Table 2).

B-cell pancreas insulin expression

The mean of β cell insulin expression intensity was found to be higher in P2 (SG + Omentoplasty) (84.25 ± 4.33) compared to P1 (SG alone) (80.73 ± 5.51) and control (74.33 ± 8.80). P1 data was abnormal (p=0.003), so we proceed to Kruskal Wallis test (Table 3). Based on Kruskal Wallis analysis, the mean difference of all groups in β cell insulin expression was significant (p=0.043). Mann-Whitney test was done to analyze significance between each group (Table 4). P2 (SG + Omentoplasty) group was statistically significant difference (p = 0.020) compared to K (control) group, according to Mann Whitney test (Table 5).

IL-1β serum level

All group has normal data analyzed from Saphiro-wilk test. The mean of IL-1β serum level was found to be lower in P2 (SG + Omentoplasty) (72.93 ± 3.69) compared to P1 (SG alone) (82.28 ± 2.91) and control (96.17 ± 1.75). so we continue to One way ANOVA test (Table 6). Based on One way ANOVA test, the mean difference of all groups in IL-1β serum level was significant (p<0.001). Levene test p=0.105 explains that the data were all homogenous. Post Hoc LSD test was done to analyze significance between each group (Table 7). From the Post Hoc LSD test result, P2 group was statistically

Table 3. β cell insulin expression descriptive data

Group	N	Mean ± SD	Median	p
K	6	74.33 ± 8.80	77 (60 – 84)	0.578*
P1	8	80.73 ± 5.51	82 (67.8 – 86)	0.003
P2	8	84.25 ± 4.33	84 (78 – 90)	0.530*

Notes: *Normal data (p > 0.05) (Shapiro-wilk)

Table 4. β cell insulin expression Kruskal Wallis Test

Group	Median (min-max)	p
K	77 (60 – 84)	0.043*
P1	82 (67.8 – 86)	
P2	84 (78 – 90)	

Notes: *Significant (p < 0.05)

Table 5. β cell insulin expression Mann Whitney test

β cell expression	P1	P2
K	0.089	0.020*
P1	–	0.280

Notes: *Significant (p < 0.05)

Table 6. IL-1β serum (10th-day) descriptive data (pg/mL)

Group	Mean ± SD	Median (min-max)	p
K	96.17 ± 1.75	96.01 (93.51 – 98.50)	0.918*
P1	82.28 ± 2.91	82.04 (78.54 – 87.52)	0.922*
P2	72.93 ± 3.69	73.55 (67.56 – 77.54)	0.490*

Notes: *Normal data (p > 0.05) (Shapiro-wilk)

Table 7. IL-1β serum (10th day) One Way ANOVA test

Group	Mean ± SD	p	Levene test (p)
K	96.17 ± 1.75	<0.001*	0.105**
P1	82.28 ± 2.91		
P2	72.93 ± 3.69		

Notes : * Significant (p<0.05); ** Homogen (p>0.05)

Table 8. IL-1β serum (10th day) Post Hoc LSD test

IL 1 – β	P1	P2
K	<0.001*	<0.001*
P1	–	<0.001*

Notes : *Significant (p<0.05)

Table 9. Normality Test Correlation Between β cell Insulin Expression and IL-1β Serum

Variabel	Mean ± SD	Median	p
β cell expression	80.26 ± 7.14	82 (60 – 90)	0.007
IL-1β	82.67 ± 9.82	81.04 (67.56 – 98.5)	0.127*

Notes : * Normal data (p > 0.05) (Shapiro-wilk)

Table 10. Spearman Correlation Test Between β cell Insulin Expression and IL-1β Serum

Variable	Median (min-max)	p	r
β cell Expression	82 (60 – 90)	0.025	-0.476
IL1 – β	81.04 (67.56 – 98.5)		

significantly different compared to P1 and K group (p < 0.001). P1 group also has significant difference, compared to K group (p<0.001) (Table 8).

Correlation between β cell Insulin Expression and IL-1β Serum Level

IL-1β serum level data was normal (p = 0.127), but β cell Insulin Expression data was not (p = 0.007). Then we proceed to Spearman correlation test (Table 9). Based on Spearman correlation test, β cell insulin expression was correlated with IL1 – β serum level (r = -0.476). Negative with moderate impact correlation (Table 10).

DISCUSSION

In our study, of 27 Sprague-Dawley rats induced by STZ-NA, all confirmed to be diabetic. Five rats died, three rats in the control group, one rat in SG-only group, and one rat in SG + Omentoplasty group. Streptozotocin (STZ) is a naturally occurring compound produced by *Streptomycetes achromogenes* with antibiotic properties that are selectively taken up by pancreatic-cells, causing its destruction. After its intraperitoneal administration, STZ behaves as a glucose analogue and is transported mainly by the glucose transporter subtype 2 (GLUT-2) into the pancreatic-cell, where it induces toxicity, mainly by producing DNA alkylation. Insulin production is compromised, as well as cell survival. GLUT-2 also expressed in other cells behind those from pancreas, the toxic action of STZ also occurring in hepatocytes and kidney cells. These are probably the reasons underlying the high mortality rate associated with this model.[18,20] However, the catastrophic side effect of STZ has been minimalized by Nicotinamide (NA), a vitamin B3 (niacin) derivate with antioxidant capacity which reduces cytotoxic actions of STZ.[18]

Diabetes, if not treated properly, increases the risk of early death. Globally, 11.3% of deaths were caused by diabetes. The IDF estimates that around 4.2 million adults died from diabetes and its complications in 2019.[21] In this study, we did not give any drugs or diet that may improve rats' glucose index status. SG and Omentoplasty were the only treatment that may intervene the diabetic outcome.

The American Society for Metabolic and Bariatric Surgery (ASMBS), Diabetes Surgery Summit 2nd Consensus Guideline (DSS-II), and the International Diabetes Federation (IDF) have agreed that bariatric procedures: adjustable gastric banding (AGB), sleeve gastrectomy (SG), roux-en-y gastric bypass (RYGB), biliopancreatic diversion (BPD), and Biliopancreatic Diversion with Duodenal Switch (BPD-DS), as diabetic operations that can be used. The findings of comparative studies and systematic reviews suggest the magnitude of the benefits and risks among metabolic surgical procedures as follows: BPD-DS> RYGB> SG> AGB. More extensive diversion procedures are generally associated with greater weight loss, greater metabolic benefits, but with a higher risk of surgical complications and malnutrition.[12]

Currently, more than 95% of bariatric procedures performed worldwide in obese and T2DM patients are SG and RYGB.[12] The RYGB procedure, nevertheless, is the first definitive procedure to demonstrate resolution of type 2 diabetes before weight loss.[13] However, In several studies, RYGB had a double-time postoperative complication rate compared to SG. In the other hand, Shorter operative time, absence of gastrointestinal anastomosis, retained pylorus, and unchanged intestinal absorption tract, contribute to the safety profile of the SG procedure. SG will also be a better choice in patients with high surgical risk.[12]

According to this study, Sleeve Gastrectomy procedure increases the β cell insulin expression (Mean 80.73 ± 5.51 compared to Mean 74.33 ± 8.80 in control) despite an insignificant outcome ($p = 0.089$). The result was seen differently in IL-1β serum level, which causes statistically significant decrease compared to control ($p < 0.001$). Suggesting the improvement in Langerhans β cell is more of a function than a histology, on the initial phase.

After SG procedure, theoretically, there will be several body metabolism changes, including increased levels of the hormone Glucagon-like Peptide-1 (GLP-1). The "Hindgut" Hypothesis said that the early presence of undigested food in the distal small bowel stimulates the secretion of "incretin" substances, which in turn determines normalization of the glycemia, increases insulin production, and decreases insulin resistance. GLP-1 is an incretin hormone secreted by enteroendocrine L cells in the small intestine which is associated in stimulating the growth of β-cells, reducing their apoptosis and, ultimately, increasing β cell mass in rats.[12,14] GLP-1 can also function as anti-inflammatory cells locally in the intestine through the involvement of the GLP-1 receptor on intestinal intraepithelial lymphocytes (Intestinal Intraepithelial Lymphocytes/IELs), or systemically in various peripheral organs through weight loss / improved glucose control, or by targeting organs and cell types that express GLP-1R. As shown by reduced plasma Interleukin-6 (IL-6) levels after GLP-1 analogs administration in a study of obese diabetic subjects.[15]

This study also revealed that combination of SG and pancreas Omentoplasty did give significant outcome in increasing β cell insulin expression ($p = 0.020$) and decreasing IL-1β serum level ($p<0.001$), compared to control. Meanwhile, if the SG and Omentoplasty group was compared to SG-only group, β cell insulin expression did not have significant result ($p = 0.280$), but have statistically significant difference in IL-1β serum level ($p < 0.001$).

The striking feature of omentum is that its volume expands in response to foreign particles and inflammation. This makes a large number of immunomodulatory cells along with cells that have the property of activated stem cells, which is called the "Omentum Activation" process. The activated omentum contains at least three different cell groups of function: CD45- cells which can suppress Th17 cells; MDSC (Myeloid-Derived Suppressor Cells) Immunomodulators CD45 +, Gr1 +; and CD45-, CD34 + type MSC (Mesenchymal Stem Cell).[17]

T cells play an important role in both the acute inflammatory process and the development of chronic fibrosis. In experimental studies, omentum works to suppress the activation and proliferation of T cells through CD45 cells - which inhibit Th17 cells. In addition, Omental Stromal Cells (OCs) were shown to reduce levels of pro-inflammatory cytokines such as IL-6 and IL-12 p40.[17]

MDSCs proliferate in the activation process of omentum and play a role in regulating inflammatory and immune responses, while MSC activation acts as a major cellular source for tissue repair activities. Recent studies have confirmed that MSC omentum is pluripotent stem cells, which can differentiate into not only mesodermal cells, but also cells from endodermal and ectodermal, including cardiomyocytes, pulmonary epithelial cells, hepatocytes, neurons, and pancreatic islets.[17]

Activated stromal omental cells (OC) are also a rich source of growth factors including fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF); both of which are key factors in inducing tissue neovascularization.[17]

The discovery of the anti-inflammatory effect of insulin can be traced back to previous studies that insulin exerts a vasodilating effect through the release of endothelial Nitric Oxide (NO) in arteries, veins and capillaries. NO release can suppress three important inflammatory mediators: Intercellular Cell Adhesion Molecular-1 (ICAM-1), MCP-1 expression, and binding of NFkB in human aortic endothelial cells in vitro.[10]

Toll-like receptors (TLRs) are various pattern-recognition receptors that are involved in the innate immune response. Accumulating evidence suggests that TRL plays an important role in inflammation and tissue damage. It has been reported that insulin infusion (2 U / hour) in T2DM patients within 2 hours significantly suppresses TLR1, -2, -4, -7 and -9 mRNA expression on mononuclear cells. Thus, insulin suppresses the expression of multiple TLRs at the transcription level and reduces TRL-mediated inflammatory injury.[10]

Investigations have been carried out to study the effect of insulin on mononuclear cells in obese non-diabetic subjects. The results showed that insulin reduced the activation of the pro-inflammatory transcription factor NFkB, by down-regulation of plasma-soluble intercellular adhesion molecules, which facilitate monocyte attachment to endothelial cells and chemotactic factor MCP-1, which promotes the migration of monocytes into

the subintimal space. Insulin suppresses pro-inflammatory transcription factors in mononuclear cells and the inflammatory mediators regulated by them, thereby decreasing inflammation caused by mononuclear cells.[10]

Based on this study, after SG and Omentoplasty procedure, β cell insulin expression intensity and IL-1β serum level negatively correlate with moderate impact (r=-0.476). It means, SG and Omentoplasty procedure have sufficient effect in resolving non-obese DMT2 rats, especially in increasing β cell insulin expression, and afterward, decreasing IL-1β serum level.

In previous non-obese DMT2 study, most of researchers prefer to evaluate the outcome of Gastric-bypass procedure, rather than SG procedure. One prospective study was found linking SG procedure in non-morbidly obese patients. The study confirms the positive impact of LSG on diabetic status of non-morbidly obese patients, possible mechanisms include the rise in post-prandial GLP-1 level induced by accelerated gastric emptying, leading to an increase in insulin secretion.[22] These outcome was similar to our study. In our descriptive data, glucose serum level improved after SG procedure. We have not found any study mentioning about pancreas Omentoplasty procedure. Our study might be a novelty procedure that encourages other researchers to do some modifying research for the better result in the future.

There are several limitations in this study, including: the animal model of diabetic induction may not reflect the true pathogenesis of Diabetes Mellitus (GK rats were not available in our lab) and the absence of long-term sample outcome (to evaluate recurrence, partial, or full remission of diabetes). However, this study shows that Sleeve Gastrectomy and pancreas Omentoplasty is a useful procedure to resolve diabetes mellitus in non-obese rats. Future research needed in order to be able to apply in humans.

CONCLUSION

Sleeve Gastrectomy and pancreas Omentoplasty could improve DMT2 in the non-obese subject. Higher β cell insulin expressions and lower IL-1β serum levels were documented in this study, with negative moderate impact correlation between them.

ETHICAL APPROVAL

Ethical Clearance for experimental animals was obtained from IEC Faculty of Medicine, Universitas Diponegoro-Dr. Kariadi General Hospital, Semarang, Indonesia. (No.84/EC/H/FK-UNDIP/IX/2020).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

DE designed the study, did the surgery procedure, collected and analyzed the data, and wrote the manuscript. AM did the conceptual idea, medical aspects, and contributed to surgery procedure. CW assisted in overall animal treatment. VM participated in surgery procedure. IR provided advice on the methodology, and reviewed the manuscript.

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