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EFFECT OF SLEEVE GASTRECTOMY WITH PANCREATIC OMENTOPLASTY ON PANCREATIC VEGF INTENSITY IN NON-OBESITY DIABETES MELLITUS RATS

Mughni Abdul, Chemy Wiryawan, Reza Tri Sutrisno, Vito Mahendra, Dimas Erlangga
Universitas Diponegoro, Indonesia
Email: dr.abdulmughnirozy@gmail.com, chemywiryawancahyono@gmail.com, reza.trisutrisno96@gmail.com, doktervito@gmail.com, mr.dimaserlangga@gmail.com

ABSTRACT

Diabetes mellitus is one of the most common non-communicable diseases that that is still growing today especially diabetes mellitus type 2 (DMT2). Diabetes in non-obese patients is an important problem to solve because it tends to be worse than DM in obese patients. Chronic hyperglycemia can damage body tissues through several mechanisms like polyol pathway, hexosamine pathway, activation of protein kinase C (PKC) and advance glycation end products (AGEs). This pathway can damage the pancreas so that insulin cannot be secreted and worsen the condition of diabetes. Sleeve gastrectomy procedure can secrete hormones such as insulin, GLP-1, PYY (Peptide YY) dan PP (Pancreatic polypeptide) which play a role in the regulation of glucose in the blood. Omentoplasty can play a role in cell regeneration, especially Langerhans β cells so that insulin can be produced adequately. Objective to evaluate the effect of Sleeve Gastrectomy and Pancreas Omentoplasty on Pancreatic VEGF Intensity in non-obese diabetes mellitus rats. Methods True experimental study with "post-test only control design" on 18 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 VEGF Intensity using immunohistochemistry. Statistical analysis with One Way ANOVA and Post Hoc LSD. Result Pancreatic VEGF increased in P1 and P2. In all groups in pancreatic VEGF levels were statistically significant (p = <0.01). Conclusion Sleeve Gastrectomy and Pancreas Omentoplasty increased pancreatic VEGF in non-obese rats with diabetes mellitus.

KEYWORDS *Diabetes Mellitus, Sleeve Gastrectomy, Omentoplasty, Pancreatic VEGF*

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INTRODUCTION

Diabetes mellitus is a chronic condition due to an increase in blood glucose levels due to a lack of the insulin hormone in the body, or the insulin hormone does not work effectively. Based on the International Diabetes Federation (IDF) as many as 463 million people in the world have diabetes mellitus and Indonesia is ranked 7th (10.7 million people).(Atlas, 2019)

There are 2 types of diabetes mellitus and 90% of cases of diabetes mellitus are type 2 diabetes mellitus (DMT2). The risk factors for DMT2 can be influenced by a combination of genetic factors associated with insulin secretion failure, insulin resistance and environmental factors such as obesity, overeating, stress and lack of exercise. Obesity is considered a frequently recognized factor in the pathogenesis of DMT2. However, in Asian countries the majority of the body mass index (BMI) population is included in the non-obese category which makes it possible that non-obese diabetes is a concern for public health policy and has a worse prognosis than diabetes with obesity (Kashima, Inoue, Matsumoto, & Akimoto, 2015),(Ozougwu, 2013)

Chronic hyperglycemia causes tissue damage, especially insulin target tissue. The mechanism of tissue damage in DMT2 is through the polyol pathway, hexosamine pathway, activation of protein kinase C (PKC) and advance glycation end products (AGEs). In the PKC pathway, intracellular hyperglycemia causes an increase in the synthesis of diacylglycerol which causes the expression of PKC in cells to also increase which will change various gene expressions as a whole and damage blood vessels (Decroli, 2019). One of the target organs damaged is the pancreas, so it will worsen the condition of DMT2 due to Langerhans cells cannot secrete insulin.

The current therapeutic management of DMT2 focuses on preventing and managing complications, not on radical therapy, because they regard DMT2 as a chronic progressive and irreversible disease. 92.7% of patients with diabetes mellitus have uncontrolled blood glucose levels. Bariatric surgery, in obese patients, results in resolution of diabetes in more than 90% of patients. The underlying mechanism is thought to be due to significant weight loss and calorie restriction. However, a large scale study with 608 patients followed for 14 years showed that resolution of diabetes occurred before significant weight loss occurred and DMT2 therapy was continued when the patient was obese. Surgical therapy has attracted attention as a therapy for non-obese DMT2 patients. Surgery has been reported to control blood glucose levels by reducing insulin requirements.(Baskota, Li, Dhakal, Liu, & Tian, 2015)

Sleeve Gastrectomy (SG) procedure affects the absorption of nutrients and secretion of metabolic hormones such as insulin, GLP-1, PYY (Peptide YY) and PP (Pancreatic polypeptide) which can significantly control blood glucose as a therapy for DMT2.(Huang, Ding, Fu, & Cai, 2019) *Omentoplasty* is a surgical procedure where the omentum major is used to cover defects, improve arterial or portal venous circulation, absorb effusions, or increase lymphatic drainage.(Pai, 2019) The omentum is an organ that moves around the peritoneal cavity and plays a role in controlling infection and contaminants. The omentum also functions as an anti-inflammatory, increasing revascularization and tissue regeneration.(Di Nicola, 2019) *Omentoplasty* has succeeded in providing a significant output in cases of hydatidiform cysts on the liver that *omentoplasty* can help the healing process and absorb serosal fluid.(Muftuoglu, Koksal, & Topaloglu, 2005) *Pancreatic omentoplasty* is expected to increase the vascularization of Langerhans cells so that it can increase secretion insulin. Insulin can act as an anti-inflammatory agent. So it is expected that insulin secretion by Langerhans cells which increases can suppress the inflammatory process in the body which will eventually decrease insulin resistance.(Sun, Li, & Gao, 2014)

There has been no study linking the combination of *Sleeve Gastrectomy* and *Pancreatic Omentoplasty* on pancreatic histology in non-obese DMT2 patients. This study will evaluate pancreatic VEGF levels in non-obese DMT2 subjects who underwent *Sleeve Gastrectomy* and *Pancreatic Omentoplasty* and then analyze the correlation between the two procedures.

RESEARCH METHOD

Animals

The subjects of this study used 18 male *Sprague-Dawley* rats, aged 6-8 weeks, weighing 170-200 grams, obtained and treated at the Integrated Research and Testing Laboratory (LPPT), Gadjah Mada University, Yogyakarta. All rats were adapted for 1 week to laboratory conditions before the study started. Rats were given a diet according to the standard.

Induction materials

Rats were injected with 230 mg/kgBW Nicotinamide (NA) intraperitoneally 15 minutes before administration of a single dose of Streptozotocin (STZ) 65 mg/kgWB intraperitoneally. On the 3rd day after induction, the rats without fasting were taken from the infraorbital vein. Serum glucose levels were measured. Glucose level ≥ 200 mg/dL is categorized as Diabetes Mellitus.

Sleeve Gastrectomy

This procedure was performed after the rats were anesthetized using an intramuscular injection of ketamine hydrochloride 20 mg/kgWB. The abdominal cavity was opened with a left oblique subcostal incision. The rat's stomach was injected with saline solution to increase the volume to make it easier to measure and cut above the greater curvature until 50% of the stomach volume remained. To minimize bleeding, clamp before the cutting line. Then closed the remaining stitches with PGA 5.0 thread.

Pancreas Omentoplasty

The rat pancreas was identified as a small tapered lump located between the duodenum and spleen. Histologically, cells were found predominantly in the tail of the pancreas, attaching to the spleen. The tail of the pancreas was closed with a pedicled-omentum, and the sheath was closed using one loose suture with PGA 5.0 suture, to avoid injury to the splenic vessels. Close the abdominal cavity with simple sutures using PGA 3.0 suture.

Experimental Design

After the rats were diagnosed with diabetes mellitus, the rats were randomly divided into 3 groups. Controls (Group K), Sleeve Gastrectomy (Group P1), Sleeve Gastrectomy and Prancreas Omentoplasty (Group P2). Body weight and serum glucose levels were measured on one day before surgery, day 5 and day 10 post procedure. Pancreatic VEGF levels were measured on day 10. Serum glucose levels were obtained with the Glucose GOD FS Kit (DiaSys). VEGF levels were measured using immunohistochemistry (IHC).

On day 10, the rats were terminated and the pancreas was extracted. Paraffin blocks were fabricated and analyzed at the Laboratory of Anatomical Pathology, Faculty of Medicine, Sebelas Maret University, Surakarta. Each sample was cut to a thickness of about 4 microns and stained with Immunohistochemistry (IHC) anti-Insulin monoclonal antibody. VEGF levels were calculated based on pancreatic -cells with the intensity of the percentage of all cells stained brown in the islets of Langerhans from a significant area with 400x microscopic magnification view in 5 different view planes, in one paraffin block. All samples were confirmed by 2 pathologists.

A B C

Figure 2

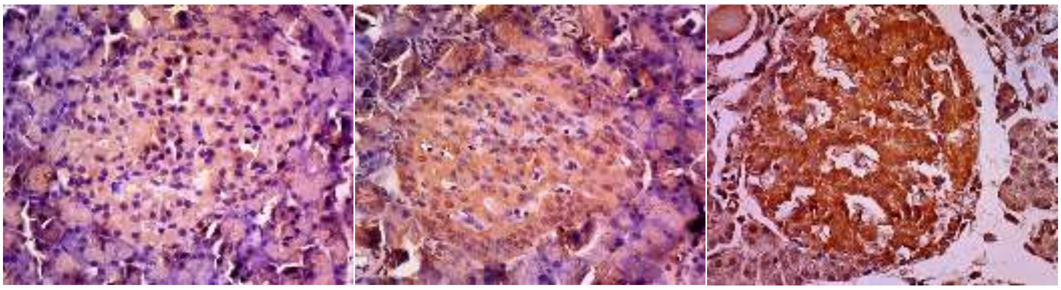
Sleeve gastrectomy procedure. A: identification of the stomach, B: removal of part of the stomach and suturing, C: closure of the left oblique subcostal incision of the abdomen

Statistic analysis

Body weight and serum glucose levels were presented descriptively in the form of mean, SD, and number of sample tables for each group. VEGF levels are presented descriptively in the form of numbers and percentages. VEGF levels on day 10 post-procedure data were tested for normality, followed by the *One Way*

ANOVA. The significance level was limited to p 0.05 with a 95% confidence interval. Data were analyzed with SPSS 20.0 software for Windows.

RESULT AND DISCUSSION



A B C

Figure 4
Pancreatic VEGF intensity. A: weak intensity (control), B: moderate intensity (SG), C: strong intensity (SG+Omentoplasty)

Sampel characteristics

18 rats that were still alive until the 10th day after treatment were analyzed. Characteristics of sample body weight and serum glucose level are presented in table 1 and table 2.

Table 1
Weight data (grams)

Day	Group	N	Mean±SD	Median
-1	K	6	177,17±5,64	176,50
	P1	6	173,83±3,06	174,00
	P2	6	174,67±4,63	175,50
5	K	6	160,67±4,50	159,50
	P1	6	157,17±2,79	157,00
	P2	6	158,17±4,45	159,50
10	K	6	144,17±6,34	143,00
	P1	6	139,33±3,14	140,50
	P2	6	142,83±6,24	143,50

The mean body weight was almost the same between all groups on the same measurement day. Weight loss was observed on day 5 and day 10 post-procedure, with the lightest weight on day 10.

Table 2
Serum glucose level data (mg/dL)

Day	Group	N	Mean±SD	Median
-1	K	6	266,54±3,99	264,59
	P1	6	264,53±3,23	264,21
	P2	6	262,61±3,05	263,00
5	K	6	271,48±2,27	271,49
	P1	6	193,66±13,61	190,67
	P2	6	179,13±5,51	180,91

10	K	6	274,76±2,81	274,32
	P1	6	174,44±7,85	177,65
	P2	6	160,51±4,41	159,41

Mean serum glucose levels were similar in all groups at pre-procedure 1 day. over time, the observed serum glucose levels showed different results between all groups. The P2 (SG + Omentoplasty) group had the best mean serum glucose improvement among the other groups, on day 10 post-procedure (160.51±4.41).

Pancreatic VEGF Level

Table 3
Pancreatic VEGF level data

Group	Pancreatic VEGF Level			N	p
	Weak	Medium	Strong		
K	6	0	0	6	0.421*
P1	0	5	1	6	0.820*
P2	0	1	5	6	0.421*
Total	6	6	6	18	

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

Strong-intensity pancreatic VEGF levels were found to be higher in P2 (SG + Omentoplasty) compared to P1 (SG) and controls. All data are normal, test the hypothesis using the *One Way ANOVA* test.

Table 4
One Way ANOVA Test Pancreatic VEGF Levels

Groups	Pancreatic VEGF Level			N	p
	Weak	Medium	Strong		
K	6	0	0	6	<0.01*
P1	0	5	1	6	
P2	0	1	5	6	
Total	6	6	6	18	

Note: * Significant (p < 0.05)

Based on the *One Way ANOVA* test, the differences in all groups in pancreatic VEGF levels were statistically significant (p = <0.01). The Post Hoc test was performed to analyze the significance between each group.

Table 5
Post Hoc LSD Test Pancreatic VEGF Level

Group	P1	P2
K	<0.01*	<0.01*
P1	-	0.003*

Note: * Significant (p < 0.05)

From the Post Hoc LSD test result, P2 group was statistically significant difference compared to P1 and K group (p < 0.01). P1 group also has significant difference, compared to K group (p < 0.01).

Discussion

In this study, of 18 *Sprague-Dawley* rats induced by STZ-NA, all were confirmed to be diabetic. Streptozotocin (STZ) is an antibiotic derived from Streptomyces achromogenes and a structural derivative of glucosamine from nitrosourea, has a selective toxic effect on pancreatic cells and causes diabetes. Streptozotocin is taken up by cells via the glucose transporter GLUT-2 and increases the production of free radicals causing DNA damage, followed by activation of the core enzyme poly(ADP-ribose) synthetase, which is involved in DNA repair. This leads to media depletion of the nuclear poly(ADP-ribose) synthetase enzyme, nicotinamide adenine dinucleotide (NAD), leading to decreased insulin synthesis in cells and cell death. This streptozotocin-induced cytotoxicity is overcome with nicotinamide, a component of NAD that inhibits poly(ADP-ribose) synthetase.(Ghasemi, Khalifi, & Jedi, 2014)

Diabetes, if not treated properly, increases the risk of premature death. Globally, 11.3% of deaths are caused by diabetes. The IDF estimates that approximately 4.2 million adults died from diabetes and complications from diabetes in 2019.(IDF Diabetes Atlas 9th edition, 2019) In this study, we did not provide any medication or diet that could improve the glucose status of rats. SG and Omentoplasty are the only intervening treatments of diabetes.

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), Rouxen-Y Gastric Bypass (RYGB), Biliopancreatic Diversion (BPD), and Biliopancreatic Diversion with Duodenal Switch (BPD-DS), as diabetes surgeries can be used. Findings from comparative studies and systematic reviews suggest the following magnitude of benefits and risks among metabolic surgical procedures: BPDDS>RYGB>SG>AGB. More extensive switching procedures are generally associated with greater weight loss, greater metabolic benefit, but with a higher risk of surgical complications and malnutrition.(Buchwald & Buchwald, 2019)

Currently, more than 95% of bariatric procedures performed worldwide in obese and DMT2 patients are SG and RYGB. The RYGB procedure is the first definitive procedure to demonstrate resolution of type 2 diabetes prior to weight loss. However, in some studies, RYGB had twice the postoperative complication rate compared to SG. On the other hand, shorter operative time, absence of gastrointestinal anastomoses, retained pylorus, and unchanged intestinal absorption tract, contribute to the safety of the SG procedure. SG will also be a better choice in patients with high surgical risk.(Buchwald & Buchwald, 2019)

According to this study, Sleeve Gastrectomy procedure improved serum glucose status (mean±SD 174.44±7.85 compared to control mean±SD 274.76±2.81). This shows that after the SG procedure, theoretically there will be some changes in the body's metabolism, including increased levels of hormones such as Glucagon-like Peptide-1 (GLP-1). The “Hindgut” hypothesis states that the presence of undigested food in the distal small intestine stimulates the secretion of “incretin” substances, which ultimately determine the normalization of serum glucose, increase insulin production, and decrease insulin resistance. GLP-1 is an incretin hormone secreted by enteroendocrine L cells in the small intestine that is associated with stimulating β cell growth, reducing apoptosis and, increasing β cell mass in rats.(Huang et al., 2019),(Buchwald & Buchwald, 2019)

In this study also used a combination of SG and Pancreatic Omentoplasty which showed an increase in pancreatic VEGF levels had statistically significant ($p = <0.01$) compared to control. Meanwhile, if the SG + Pancreas omentoplasty was compared with the SG group, the VEGF level have a significant result ($p = 0.003$).

Omental adipocytes are the main source of VEGF protein. VEGF can induce angiogenesis and neovascularization. In experimental animals it was reported that the omental vascular anastomosis with the intestinal wall could form as early as the third day after surgery. In addition, hypoxia can lead to increased VEGF expression in omental adipocytes. Omentoplasty can protect the disrupted anastomosis by providing a biological space to prevent leakage and a source of granulation tissue and neovasculature for wound repair.(Tuo et al., 2020)

Based on this study, after SG and Omentoplasty, pancreatic VEGF levels were higher than controls. That is, the SG procedure and Omentoplasty have sufficient effect in resolution in non-obese rats with DMT2, especially in repairing Langerhans cells thereby increasing insulin secretion and decreasing insulin resistance.

There are some limitations to this study, namely that induction from animal models of diabetes may not reflect the true pathogenesis of Diabetes Mellitus and the absence of long-term sample outcomes (evaluating relapse, partial or complete remission of diabetes). However, this study shows that sleeve gastrectomy and pancreatic omentoplasty are useful procedures for treating diabetes mellitus in non-obese rats. Future research is needed to make it applicable to humans

CONCLUSION

Sleeve Gastrectomy and Pancreas Omentoplasty can improve type 2 Diabetes Mellitus status in non-obese rat subjects. SG + pancreatic omentoplasty increases pancreatic VEGF levels.

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