Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2023; 40(1): 27-30
doi: 10.52142/omujecm.40.1.6

HOMA-IR level in obese type 2 diabetic rat model treated by Sleeve gastrectomy and pancreatic omentoplasty

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Received: 04.09.2022 • **Accepted/Published Online:** 26.11.2022 • **Final Version:** 18.03.2023

Abstract

Obesity is a health problem that occurs due to the wrong lifestyle, such as lack of physical activity and the wrong diet. Accumulation of adipose tissue in obesity may increases pro-inflammatory cytokines, particularly in pancreatic beta cells leading to type 2 diabetes mellitus (T2DM). Sleeve gastrectomy (SG) is an alternative therapy for T2DM in obese patients by losing about 40-60% of body weight and increasing GLP-1 secretion which stimulates increased insulin secretion. However, the SG procedure cannot reduce pro-inflammatory cytokines which promote damaged pancreatic cells. Pancreatic omentoplasty can suppress pro-inflammatory cytokines and promote the regeneration of damaged pancreatic cells. The goal of this study is to investigate HOMA-IR in obese rats with diabetes mellitus who underwent SG and pancreatic omentoplasty procedures. An experimental using pre and post-test control group design were done in this study. Eighteen Diabetes Mellitus rats were divided into 3 groups: K1 (SG), K2 (SG + Omentoplasty), and K3 (control). Blood glucose and insulin level were measured using a glucoDR Glucometer Bio-sensor kit and ELISA, respectively before and 10 days after the procedure. HOMA-IR measurement was calculated based on insulin and blood glucose level. A significant decrease of fasting blood gluocese levels were shown in all treatment groups of this study after day 10^{th}. There was a significant increase in the insulin levels after day 10^{th}. Highest decrease of the blood glucose levels and increase of the insulin levels were shown in group K2. Furthermore, a significant decrease of HOMA-IR was shown in the K2 on day 10^{th}. From this study, we may conclude that SG and Pancreas Omentoplasty may significantly reduce the HOMA-IR value in obese rats with T2DM.

Keywords: obesity, diabetes mellitus, gastrectomy, omentum, insulin resistance

1. Introduction

In both developing and developed countries, obesity-related problems are still a challenge for public health. Obesity can occur due to unhealthy lifestyle factors such as lack of physical activity, unbalanced diet, and hereditary factors may be responsible in obesity (1). The accumulation of adipose tissue can increase the secretion of pro-inflammatory cytokines that cause impaired secretion of hormones such as insulin, resulting in insulin resistance. To reduce the risk of diabetes mellitus type 2 (T2DM), a weight loss program can be carried out, this program can also be carried out to improve insulin resistance. However, carrying out this program requires a long time and if patients do not have compliance to run this program, the results obtained will not be optimal (2).

Bariatric surgery such as sleeve gastrectomy (SG) could be an alternative therapy for T2DM in obese patients. This procedure results in weight loss of about 40-60% in almost 75% of patients and complete remission. However, this bariatric procedure is not accompanied by a decrease in pro-inflammatory cytokines so additional procedures are needed to reduce pro-inflammatory cytokines (3). Omentum is adipose tissue that can act as a defense agent to suppress inflammation and increase cell regeneration (4). This tissue can be used as an adjuvant in bariatric procedures to obtain optimal results. The omentum has a role in regulating T cells or Visceral Adipose Tissue (VAT), thereby increasing the expression of chemokine receptors, such as CCR1 and CCR2, and anti-inflammatory cytokine, including IL-10 leading to local immune responses regulation (5).

Measurement of insulin resistance plays an important role in the development of basic science and clinical practice. The gold standard for measuring insulin resistance is the euglycemic hyperinsulinemia clamp, however, it has a complicated procedure that makes it difficult to apply to large-scale tests. Another indicator for determining insulin resistance is the homeostasis model assessment-insulin resistance (HOMA-IR).

This study performed an animal model in obese rats with T2DM that underwent SG and omentoplasty procedures as surgical therapy for diabetes mellitus in obese patients to improve insulin resistance.

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2. Materials And Methods

2.1. Animals

Eighteen male Sprague-Dawley rats aged 6-8 weeks with a body weight of 170-200 grams, (6) were adapted for 1 week using a standard diet at the Integrated Research and Testing Laboratory (LPPT), Gadjah Mada University, Yogyakarta.

2.2. Animal adaptation

The rats were treated and kept clean from pathogens every day and the substrate for the rats, namely sawdust, was replaced twice a week. Rats were kept at 24±4°C room temperature, 50% relative humidity, and 12:12-hour light-dark cycle according to laboratory standards for animal models (Fig. 1). Nutritional content was adjusted using Teklad Global 14% Protein Rodent Maintenance Diet 2014S feed from HarlanTM Laboratories (2014). Drinking was given ad libitum. The time for adaptation was carried out for 7 days, then fattening with High-fat feed was carried out for 4 weeks and weighed and then assessed by the Lee Index. Rats were obese if the Lee index was more than 300.

Fig. 1. Mouse adaptation

2.3. Diabetes induction

Nicotinamide (NA) at a dose of 230 mg/kg was injected intraperitoneally. A single dose of 65 mg/kg of Streptozotocin (STZ) was administered intraperitoneally 15 minutes after the NA injection. Diabetes mellitus status was measured using the glucoDR Glucometer Bio-sensor kit. Measurements were made by fasting for 4-6 hours. Rats were declared diabetic if their fasting blood glucose was more than 126 mg/dL (7).

2.4. Experimental design

After confirming the status of diabetes and obesity, the mice were randomly divided into 3 groups. Rats underwent Gastrectomy (K1), Gastrectomy, Pancreatic Omentoplasty (K2), and control (K3) procedures. Body weight, fasting blood glucose, and fasting insulin was measured a day before surgery and 10 days after the procedure.

2.5. Sleeve gastrectomy procedure

Before surgery, mice were fasted for about 10 hours. Injection of ketamine 20 mg/kg BW was done intramuscularly. The fur on the abdomen was washed using a hair clipper until the skin of the rat is visible. Asepsis and antisepsis were performed in the operating area. A left subcostal transverse incision was made starting from the xiphoid process to the lateral abdomen. The incision was deepened from the cutis, subcutis, and muscle to the peritoneum and intraperitoneal cavity. Gastric identification was performed (Fig. 2), followed by partial gastrectomy along the major curvature with clamps first to minimize bleeding. Gastric suturing was performed with polyglycolic acid 5.0 (Fig. 3)

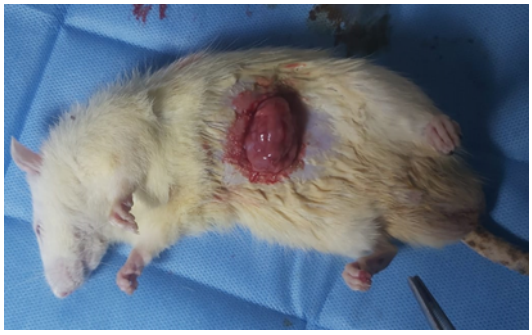

Fig. 2. Gastric identification

Fig 3A. Gastric clamping

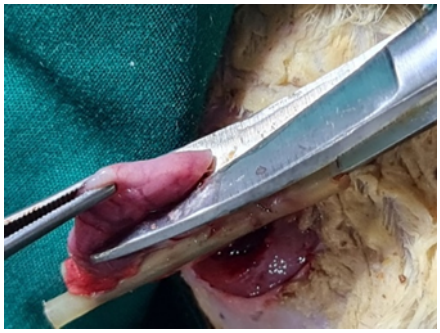

Fig 3B. Gastric cutting

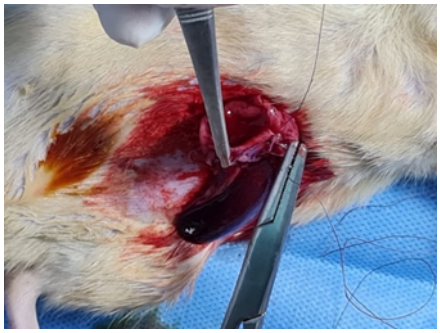

Fig 3C. Gastric suturing

2.6. Pancreatic omentoplasty procedure

The free omentum was sutured 1 piece of a suture in the body of the pancreas so that the omentum was attached to the pancreas with PGA 5 sutures (Fig 4). Bleeding was controlled with pressure gauze or sutures. The surgical wound was

sutured with PGA 5.0 thread. The wound was cleaned with 0.9% NaCl and smeared with Povidone Iodine (Fig 5).

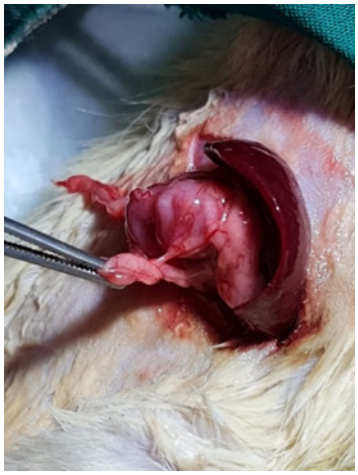

Fig. 4. Omentoplasty

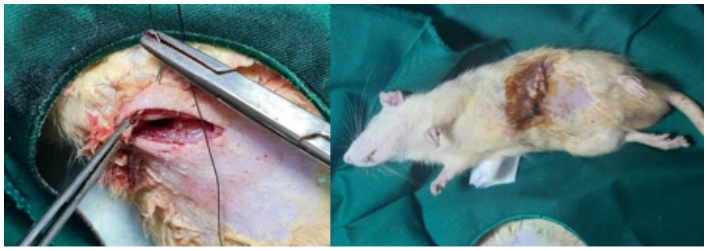

Fig. 5. Abdominal closure

2.7. HOMA-IR measurement

Insulin level were measured from blood serum samples collected at day 10 using ELISA kit. The HOMA-IR value was obtained from the analysis of insulin and blood glucose levels. HOMA-IR measured by using formula={fasting glucose (mmol/L) x fasting insulin (µU/L)}/22.5.

2.8. Statistical analysis

Body weight, fasting glucose levels, and fasting insulin were shown in the form of mean±SD. Shapiro-Wilk was used for the normality test. The HOMA-IR value was hypothesized using repeated ANOVA. Difference between groups were analyzed using Bonferonni post-hoc test. A P<0.05 was considered statistically significant.

3. Result

3.1. Animal experimental models

Eighteen diabetic and obesity rats were successfully made after induced with NA and divided into three groups evenly. After surgical treatment, body weight in treatment groups was decreased on day 10. The K2 group has an optimum decreased body weight level (Table 1). The K2 groups showed earlier effect after treatment than another group.

Table 1. Description of weight data (grams)

Group	N	Mean±SD	
		Pre	Post
K1	6	248.50±1.67	205.83±1.90
K2	6	250.83±2.02	194.50±1.96
K3	6	244.65±2.82	239.17±2.93

3.2. Fasting blood glucose

Fasting blood glucose were measured using ELISA to investigate the suppressing capacity of SG and omentoplasty after 10 days treatment. All intervention groups showed a significant reduction in blood glucose levels compared to the control group (p<0.05; Table 2). The K2 group showed the highest reduction in fasting blood glucose levels.

Table 2. Description of fasting blood glucose data (mg/dL)

Group	N	Mean±SD		p
		Pre	Post	
K1	6	265.34±2.37	188.50±2.28	0.000*
K2	6	260.94±0.72	145.29±1.44	
K3	6	265.48±0.82	268.98±0.86	

* p: repeated ANOVA followed by Bonferroni's post hoc test

3.3. Fasting insulin

To investigate the capacity of SG and omentoplasty in enhancing fasting insulin, the level of insulin in serum was analyzed using ELISA in day 10th. All intervention groups showed a significant increase in insulin levels (p<0.05; Table 3). The K2 group showed the optimum increase in insulin levels.

Table 3. Description of fasting insulin data (µU/L)

Group	N	Mean±SD		p
		Pre	Post	
K1	6	421.09±2.37	458.28±3.20	0.000*
K2	6	412.79±0.79	467.57±2.53	
K3	6	408.77±1.26	405.15±0.89	

* p: repeated ANOVA followed by Bonferroni's post hoc test

3.4. HOMA-IR value

HOMA-IR value were measured in SG and omentoplasty group. A significant decrease in all treatment groups were shown in this study (p<0.05; Table 4). While the K2 group showed the maximum reduction in the level of HOMA-IR.

Table 4. Description of HOMA-IR value data

Group	N	Mean±SD		p
		Pre	Post	
K1	6	5.86±0.06	4.54±0.05	0.000*
K2	6	5.66±0.01	3.57±0.02	
K3	6	5.86±0.06	5.73±0.02	

* p: repeated ANOVA followed by Bonferroni's post hoc test

4. Discussion

STZ induction can lead to pancreatic beta cell damage by mimicking a glucose analog and entering pancreatic cells via the subtype 2 glucose transporter (GLUT-2) which induces toxicity by producing DNA alkylation. Nicotinamide (NA) was given to prevent damage and reduce the destruction of pancreatic beta cells. Administration of a high-fat diet and induction of STZ-NA in a mouse model of T2DM could form obesity and insulin resistance (8, 9).

Based on this study, there was a decrease in blood glucose levels in the K1 and K2 groups. The sleeve gastrectomy procedure affects hormone metabolism in the body, one of which is Glucagon Peptide-1 GLP-1. GLP-1 is a peptide hormone secreted by the intestine, ileum, colon, and certain neurons in the CNS nucleus via enteroendocrine L cells. This hormone could play a role in the metabolism of vital hormones in the body and affect appetite through anorexigenic processes, delaying gastric emptying, and reducing food intake. GLP-1

could decrease blood sugar levels and improve glucose tolerance by increasing insulin secretion by inhibiting pancreatic cells and stimulating pancreatic cells, thereby causing a decrease in postprandial hyperglycemic status and insulin resistance. Increased glucose metabolism by SG was associated with increased GLP-1 secretion (10).

This study also showed that sleeve gastrectomy and pancreatic omentoplasty performed an optimum decrease in blood sugar levels, increasing insulin secretion, and reducing insulin resistance as assessed by the HOMA-IR. The K2 has optimum HOMA-IR decrease. This result showed that pancreatic omentoplasty can provide an optimal role in improving insulin resistance conditions. The function of the omentum itself is as a growth factor, neurotrophic and hemostatic factor, and an inflammatory mediator. Pluripotent stem cells are found in the omentum which can differentiate into various types of cells. Recent studies have shown that in the omentum there are multipotent-mesenchymal stem cells (MSCs) and myeloid-derived suppressor cells (MDSCs) which act as anti-inflammatory agents and immunomodulators. In addition, omentum could improve the wound healing process through the process of tissue regeneration. Several authors have described that MSCs in the omentum also differentiate into endodermal and ectodermal cells which include pancreatic islets (4).

There are several limitations to this study. In this study, inflammatory cytokines such as IL-6, IL-10, and TNFα were not analyzed to investigate the exact mechanism of insulin resistance improvement. Relevant serum hormone levels like GLP-1 were also not performed in this study, which may give a better understanding of insulin resistance enhancement. More futur studies may be needed to assess the combination of its surgical procedure to continue to the clinical study.

SG and Pancreatic Omentoplasty could reduce insulin resistance in obese T2DM rats. SG and Pancreatic Omentoplasty could reduce blood glucose levels, increases insulin secretion, and reduce insulin resistance as seen from the HOMA-IR value.

Ethical statement

All laboratory and animal procedure were done under the standard guideline for animal experimental studies. This study was approved by the Ethics Committee of Health Studies, Faculty of Medicine, Universitas Diponegoro (Ethical clearence number: 51/EC/H/FK-UNDIP/V/2021).

Conflict of interest

The authors declare no competing interest in this study.

Funding

No external and public funding were used in this study.

Acknowledgments

The authors wish to thank the Director of Kariadi Hospital Semarang and Head of Digestive Surgery Department – Medical Faculty of Diponegoro University Semarang.

Authors' contributions

Concept: A.M., V.M.E., Data Collection or Processing: R.T.S, A.T.P, Analysis or Interpretation: I.P., D.E., Literature Search: A.M., V.M.E., I.P., Writing: A.M., V.M.E.

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