Original Article

Sleeve Gastrectomy and Pancreatic Omentoplasty improve β-cell status in Rats by increasing VEGF, PDX1, islet of Langerhans area, and β-cell count

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ABSTRACT

OBJECTIVE: To analyze the effect of sleeve gastrectomy and pancreatic omentoplasty on pancreatic β cell status by evaluating the levels of PDX1 and VEGF.

METHODOLOGY: This experimental animal research was done with a post-test-only control design. This research was conducted at the Laboratory of Integrated Research and Development, Universitas Gadjah Mada, Yogyakarta, Indonesia, from April to June 2022. The subjects consist of obese and T2DM rats, divided into sleeve gastrectomy (K1), sleeve gastrectomy with pancreatic omentoplasty (K2), positive control (K3), and normal rats in negative control (K4). On the 10th day post-surgery, VEGF and PDX1 were measured using polymerase chain reaction, with histologic examination of the Langerhans islet area and pancreatic β-cell count.

RESULTS: Significant differences in Langerhans islet area and pancreatic β-cell count were found between K1 and K2, and K2 and K3 ($p < 0.01$). PDX1 expression was highest in K4, followed by K2, K1, and K3, with significant differences between K4 and K3, K2 and K3, and K1 and K3 ($p < 0.01$). VEGF expression in K2 was significantly higher than in K1 ($p = 0.006$), K3 ($p = 0.004$), and K4 ($p = 0.001$).

CONCLUSION: Sleeve gastrectomy and pancreatic omentoplasty improve pancreatic β-cells status by increasing VEGF, PDX1, Langerhans islet area, and pancreatic β-cell count compared to sleeve gastrectomy alone.

KEYWORDS: Obesity, type 2 diabetes mellitus, sleeve gastrectomy, pancreatic omentoplasty, VEGF, PDX1, Langerhans islet, pancreatic β-cell

INTRODUCTION

Based on global data in 2015, 39% or 609 million out of 1.9 trillion population suffer from overweight and obesity[1]. The prevalence of obesity is predicted to increase from 14% in 2020 to 24% by 2035 [2]. Research in Indonesia stated that the prevalence of obesity and central obesity is 23.1% and 28%, respectively, with a BMI of ≥25 kg/m^2 used to define obesity[3]. Therefore, obesity has become the main priority in managing public health issues due to its various complications[4,5].

Adipose tissue accumulation in obesity can cause decreased vascularization, leading to tissue hypoxia and stimulating inflammatory response and insulin resistance. The inflammation stimulates various cellular mechanisms, including macrophage infiltration, decreased adiponectin, increased leptin, adipocyte apoptosis, endoplasmic reticulum stress, fibrosis, and mitochondrial damage in white adipose tissue (WAT) [6]. Evaluation of proinflammatory cytokines such as monocyte chemotractan protein (MCP-1) and plasminogen activator inhibitor (PAI) can be used to know the effect of tissue hypoxia. In recent years, WAT has been known to secrete some substances which regulate metabolic homeostasis, including leptin, adiponectin, resistin, tumor necrosis factor (TNF-α), IL-6, MCP-1, PAI-1, angiotensinogen, visgatin, retinol-binding protein-4, serum amyloid A (SAA), etc[7].

Laparoscopic sleeve gastrectomy (LSG) is a bariatric surgery procedure by resecting 80% of the stomach, starting at 3-6 cm from the pylorus, cutting along the primary curvature until the fundus to create a structure resembling a cylinder, measured with a 32-60 French-sized bougie. In Northern America, LSG is the most commonly performed bariatric surgery procedure, and it shows a significant effect in managing diabetes compared to gastric bypass in mid-follow-up. Almost 75% of the patients had complete remission and improved diabetic status. Moreover, the estimated

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doi: 10.22442/jlumhs.2025.01179
Received: 31-07-2024 *Revised: 26-11-2024*
Accepted: 04-12-2024 *Published Online: 03-02-2025*

weight loss after LSG is 40-60%, and BMI reduction is 8-10 kg/m^2.[8]

The antidiabetic effect in LSG has not been understood clearly, but some proposed hypotheses exist. LSG may modify neurohormonal pathways, which leads to hormonal changes in the guts, such as decreased ghrelin and peptide YY, increased incretin (glucagon-like peptide-1), bile acids, and the microbiome in a way that promotes body weight reduction, increased insulin production and sensitivity, and improve glycemic control[9]. However, 25% of cases of patients experiencing LSG have not shown significant improvement in optimal insulin production. This condition may be mediated by pancreatic fat accumulation, leading to local tissue inflammation, β-cells injury and apoptosis, causing sub-optimal insulin production. Thus, an effort is needed to resolve pancreatic inflammation and stimulate β-cell regeneration[10].

Omentoplasty is a surgical procedure that attaches the omentum to a specific abdominal organ. This surgery aims to close defects, increase arterial and venous circulation, and increase lymphatic drainage. The omentum is referred to as "abdominal police" because it protects inflamed abdominal organs and helps to revascularize organs with compromised blood vessels. Greater omentum has antibacterial, hemostatic, angiogenic, and adhesive properties, promoting tissue repair and preventing organ perforation[11,12]. Moreover, the greater omentum has a role in cell regeneration and in vivo incubators. These vast abilities of greater omentum have been applied in various surgical techniques[11].

Neovascularization is the most crucial ability of the omentum, as it stimulates neoangiogenesis in the attached organ and the surrounding structure. Some research has found that *human omental microvascular endothelial cell* (HOME *cells*) in the omentum expresses angiogenic peptides such as b-FGF and VEGF, which are the key factors in promoting neovascularization[11].

Pancreatic duodenal homebox 1 (PDX1) is a transcription factor important in evaluating pancreatic β-cells function and survival. Severe PDX1 deficiency causes pancreatic agenesis. Meanwhile, partial PDX1 deficiency causes β-cell dysfunction and apoptosis, which leads to diabetes. Chronic hyperglycemia and dyslipidemia in type 2 diabetes lead to β-cell dysfunction, which can be evaluated by PDX1 expression[13,14].

This study aims to analyze the effect of sleeve gastrectomy and pancreatic omentoplasty on pancreatic β-cell status in rats by evaluating the levels of PDX1 and VEGF.

METHODOLOGY

This experimental animal research was conducted with a post-test-only control design. All experimental animals were treated following ARRIVE guidelines and European Union Directive 2010/63/EU for animal experiments and were also approved by the Ethics Committee, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia (No. 75/EC/H/FK-UNDIP/VII/2021). This research was conducted at the Laboratory of Integrated Research and Development, Universitas Gadjah Mada, Yogyakarta, Indonesia, from April to June 2022. The subjects were 24 male Wistar rats (*Rattus norvegicus*), aged 2-4 weeks and weighed 150-200 grams. The sample size calculation was based on WHO guidelines, considering dropouts during the research. Then, the rats were adapted and given standard feed for 1 week.

Eighteen rats were fed a high-calorie and high-fat (HCF) diet for 4 weeks consisting of com feed pars 60%, wheat flour 27.8%, pork fat 10%, cholesterol 2%, cholic acid 0.2%, and fructose 2 mL/rat/day. After 4 weeks, these rat groups were injected with intravenous streptozotocin (STZ) 40 mg/kgBW for five consecutive days and provided with 30% sucrose solution ad libitum. Meanwhile, six rats were given standard food and not injected with STZ.

Eighteen rats meeting the criteria for obesity (Lee index >300) and diabetes mellitus (fasting blood glucose level >126 mg/dL) were randomly assigned into three groups labelled as K1 (which were treated with sleeve gastrectomy), K2 (which were treated with the combination of sleeve gastrectomy and pancreatic omentoplasty), and K3 (positive control group; which were not given any treatment). Six rats that were neither obese nor diabetic were assigned to K4 (the negative control group, which was not given any treatment).

Surgery was performed on K1 and K2 subjects under general anesthesia using ketamine 20 mg/kgBW intramuscularly. A left subcostal incision was made. The stomach was identified for sleeve gastrectomy, and a clamp was applied parallel to the direction of significant curvature from the pyloric antrum to the fundus. The stomach was cut until 20-30% volume remained, the clamp was released, and the resection line was sutured with PGA 3.0. For pancreatic omentoplasty, the omentum and pancreas were identified. A single stitch was made on the pancreatic body to attach the omentum to the pancreas with PGA 5.0 sutures. Then, the incision was closed with PGA 3.0 sutures.

All rats were euthanized on day 10 after surgery, followed by evaluation of PDX1 and VEGF using reverse transcription-polymerase chain reaction (RT-PCR). A pancreas sample weighing 100 mg was taken and cut into small, fine pieces, then placed into a tube containing 50 mL of RNAiso Plus. The pancreas pieces were ground using a micropestle, and an additional 50 mL of RNAiso Plus was added before incubation at room temperature for 5 minutes. Then, 20 mL of chloroform was added, and the

solution was vortexed until it became milky white. It was then incubated at room temperature for 2-3 minutes and centrifuged at 15,000 rpm for 15 minutes at 4°C, separating the solution into three layers. The top layer (liquid phase) contained RNA, the middle layer (semi-solid phase) contained DNA, and the bottom layer contained cell debris. The top layer was transferred to a new centrifuge tube, its volume was measured, and an equal volume of isopropanol was added. The Eppendorf tube was gently shaken until white threads appeared, followed by centrifugation at 15,000 rpm for 10 minutes at 4°C. The supernatant was discarded, leaving a white pellet at the bottom of the tube. After drying, 100 mL of 70% ethanol in diethyl pyrocarbonate (DEPC)-treated water was added, the tube was inverted repeatedly, and the mixture was centrifuged at 15,000 rpm for 5 minutes at 4°C. The supernatant was discarded, and 30–50 µL of DEPC-treated water was added. The mixture was incubated at 55°C for 10 minutes, yielding the total RNA solution stored at -80°C. RNA was quantified using a Nanodrop™, and the quantification results were adjusted to 3,000 ng. For cDNA synthesis, mixture A was prepared by combining the calculated RNA sample, 1 µL of OligoDT, and PCR water to reach a final volume of 10 µL. This mixture was incubated at 70°C for 5 minutes. Then, mixture B was prepared by combining 4 µL of 5X buffer, 5 µL of DEPC-treated water, and 1 µL of ReverTraAce. Mixture A was then combined with mixture B and incubated at 25°C for 5 minutes, 42°C for 50 minutes, and 85°C for 5 minutes.

Table I: Primer Sequences Used to Analyze VEGF and PDX1 in RT-PCR

Gene	Primers
VEGF	F: CTG CTG TGT TGG GTG CAC TGG R: GGT TTG ATC CGC ATA ATG TGC AT
PDX1	F: GAG GTG CTT ACA CAG CGG AA R: GGG CCG GGA GAT GTA TTT GT

The mRNA expression of VEGF and PDX1 was analyzed using RT-PCR. The mixture consisted of 3 µL of cDNA sample, 12.5 µL of Taq master mix (including dNTPs (deoxynucleotide triphosphates), Taq DNA polymerase, reaction buffer, and $MgCl_2$), 0.6 µL of specific primers (forward and reverse) for each target gene, and 8.3 µL of nuclease-free water. The primers used for the reaction are shown in **Table I**. Then, the PCR product was analyzed using electrophoresis with a 2% agarose gel and gel stain as the loading dye. The gel was subsequently documented using a gel documentation system (*gel doc*), and the density of each band was analyzed using image analysis software.

In addition, each rat's pancreatic tissue was taken and histologically processed to evaluate the Langerhans islet area and β-cell count. Histological observations of Langerhans islet were conducted using hematoxylin -eosin staining. Langerhans islets are clusters of endocrine glands scattered throughout the pancreas, resembling islands and traversed by many capillary blood vessels. In HE staining, the Langerhans islets will appear paler than other cells, making them easier to observe. Immunohistochemistry staining was conducted for the evaluation of pancreatic β cell count. The primary antibody used was mouse anti-insulin, the secondary antibody was biotinylated goat anti-polyvalent, and the chromogen was 3,3'diaminobenzidine (DAB). All brown-coloured cells (representing pancreatic β cells) were counted per 100 cells from significant areas under 40x magnification on five fields of view for each slide within one paraffin block, and the average percentage was calculated. Two researchers and one pathology expert performed histology evaluation with 95% clinical agreement.

The data were processed using the Statistical Product and Service Solutions (SPSS) program Ver. 20.0 for Windows. Descriptive data analysis was presented as mean tables, standard deviations, and box plots. The normality of data was tested using the Shapiro-Wilk test. Differences in data were tested using one-way ANOVA between each group to see if the data were normally distributed. If the assumptions of parametric tests were not met or the data were not normally distributed, the Kruskal-Wallis non-parametric test was used, followed by the Mann-Whitney test. Correlation between variables was conducted using Pearson's correlation test if the data were normally distributed, and if not, Spearman's correlation test was used.

RESULTS

Body Weight

Based on the Paired-Sampled T-Test, it was found that there was a significant difference between the weight of D0 and D10 in group K1 ($p<0.001$) and K2 ($p<0.001$). However, no significant differences were observed in groups K3 ($p=0.819$) and K4 ($p=0.280$). In Pooled T-test, an important difference was found between groups K1 and K2 with $p = 0.001$ (mean 239.17 and 205.83).

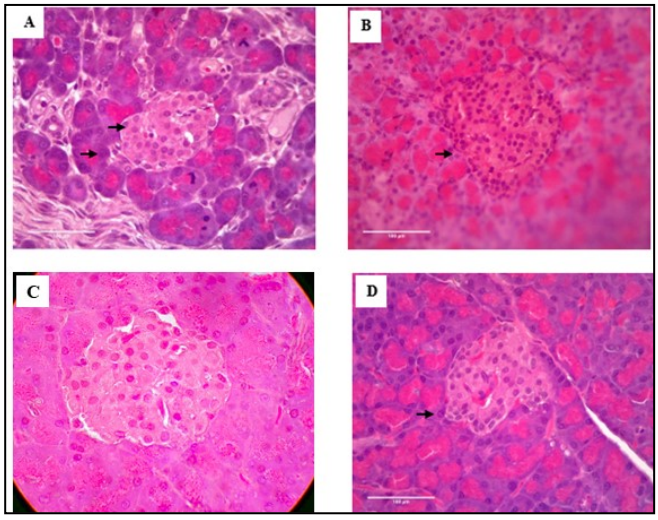
The effect of sleeve gastrectomy combined with pancreatic omentoplasty in obese rats with T2DM on pancreatic β-cell status

The status of pancreatic β-cells can be assessed by Langerhans islets area, pancreatic β-cell count, and levels of PDX1 and VEGF in the pancreas.

Langerhans Islet Area

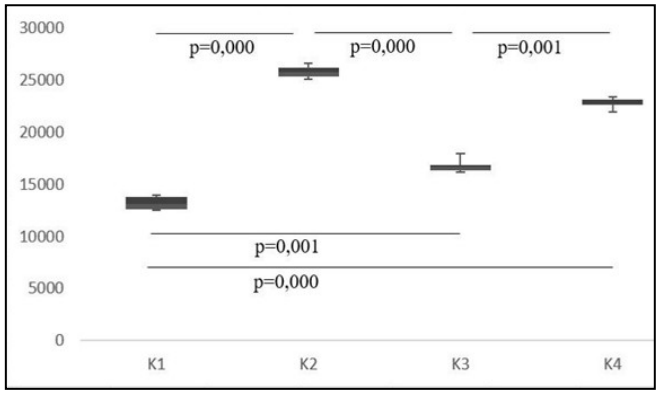
In this study, histological examination of the rat pancreas at D10 after surgery was observed following treatment. **Figure I** shows the visualization of pancreatic histology in this study.

Figure I: Histological Examination of Langerhans Islet in Each Group (100x magnification)



Notes:
A: subjects with obesity and type 2 diabetes which underwent sleeve gastrectomy
B: subjects with obesity and type 2 diabetes which underwent sleeve gastrectomy and pancreatic omentoplasty
C: subjects with obesity and type 2 diabetes (positive control)
D: subjects without obesity and type 2 diabetes (negative control)
100x magnification. Arrows (à): Langerhans islet
Langerhans islet area on day 10 post-surgery, based on the results of Post Hoc analysis, showed significant differences in groups K1 and K2 with $p < 0.01$. Significant differences were also found between groups K2 and K3 with $p < 0.01$. However, no significant difference was found between groups K2 and K4 with $p = 0.058$. The data is presented as a boxplot diagram in **Figure II** below.

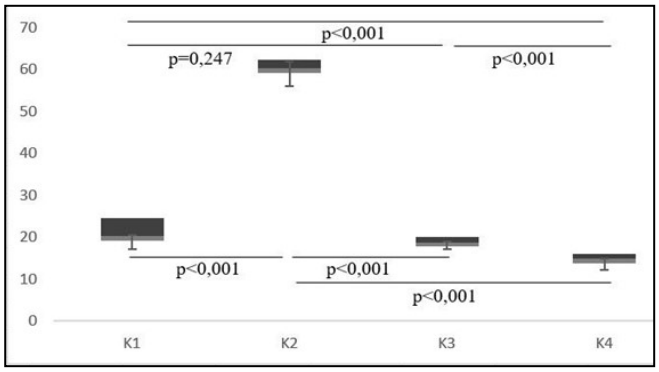
Figure II: Post Hoc LSD Test of Langerhans Islet Area (mean ± SD)



Pancreatic β-Cell Count

Based on Post Hoc analysis of pancreatic β-cell count on D10 post-surgery, significant differences were found between groups K1 and K2 with $p<0.01$ and between groups K2 and K3 with $p<0.01$. However, no significant difference was found between groups K1 and K3 with $p=0.247$. The data is presented as a boxplot diagram in **Figure III** below.

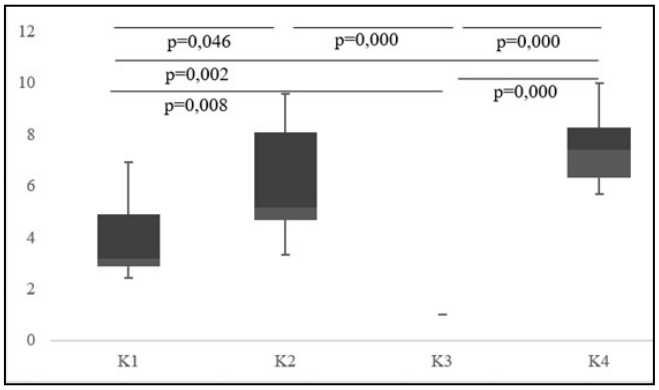
Figure III: Post Hoc LSD Test of Pancreatic β-cell Count (mean ± SD)



PDX1

The mRNA expression of PDX1 in group K4 is higher compared to group K3 ($p < 0.01$), group K2 is higher compared to group K3 ($p < 0.01$), and group K1 is higher compared to group K3 ($p = 0.008$). The positive control group (K3) expressed the lowest levels of PDX1 compared to the other groups. Based on the obtained data, the order of PDX1 expression from highest to lowest is group K4, K2, K1, and K3. The data is presented as a boxplot diagram in **Figure IV** below.

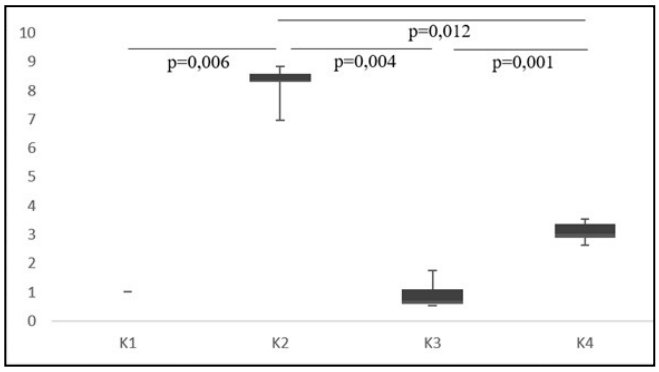
Figure IV: Post Hoc LSD of PDX1 mRNA Expression (mean ± SD)



VEGF

The LSD analysis results show that mRNA expression of VEGF in group K1 is lower compared to group K2 ($p = 0.006$), group K3 is lower compared to group K2 ($p = 0.004$), and group K4 is higher compared to group K3 ($p = 0.001$). Rats that underwent sleeve gastrectomy and pancreatic omentoplasty (K2), experiencing obesity and T2DM, actually expressed higher levels of VEGF compared to the positive control group (K3), negative control (K4), and rats with obesity and T2DM that underwent sleeve gastrectomy alone (K1). The data is presented as a boxplot diagram in **Figure V** below.

Figure V: Post Hoc LSD of VEGF mRNA Expression (mean ± SD)



DISCUSSION

Insulin resistance in type 2 diabetes mellitus (T2DM) leads to hyperinsulinemia as a form of compensation by pancreatic β-cells, increasing insulin production against the decreased functional capacity of insulin to mobilize glucose into the cells. This maladaptive cycle results in a progressive decrease in the number and function of β-cells due to necrosis and apoptosis of β-cells. Damage to pancreatic β-cells is thought to occur due to oxidative stress and endoplasmic reticulum stress as β-cells attempt to secrete insulin in large quantities, weakening the cells' defense against chronic subacute inflammation due to obesity[15]. Therefore, preserving and restoring the function of pancreatic β-cells may be a novel strategy for preventing and/or managing T2DM.

This study demonstrates that the group undergoing sleeve gastrectomy and pancreatic omentoplasty has more pancreatic β-cells and a larger area of Langerhans islets than the other groups. This finding follows the latest study about the omentum's ability in cell regeneration conducted by Zhang Y 2020[16] Stem cells in the omentum can differentiate into islet cells capable of producing insulin. Additionally, mesenchymal stem cells in the omentum can enhance insulin receptor phosphorylation and expression of glucose receptor GLUT-4 in adipose tissue and skeletal muscle, further supporting glucose mobilization into cells and improving insulin resistance[17].

Furthermore, an increase in VEGF was found in the group undergoing sleeve gastrectomy and pancreatic omentoplasty. The latest studies also have similar results[18]. Adipose cells in the omentum can produce VEGF, which stimulates the formation of new blood vessels. Angiogenesis can enhance tissue vascularization, thus supporting the repair and regeneration of pancreatic β-cells[18].

Among the two main pathways of endocrine progenitor cell formation towards glucagon-producing α cells or β cells, factors determining the balance in these pathways include transcription factors ARX and PAX4. The transcription factor MAFA is required to mature the β-cell phenotype, characterized by insulin biosynthesis expression and glucose-regulated release mechanisms. Continued expression of several genes, including the PDX1 gene, is required to maintain the mature β-cell identityx[19]; this is consistent with the research conducted, showing that PDX1 gene expression is more abundant in obese and DMT2 rats undergoing sleeve gastrectomy and pancreatic omentoplasty procedures (K2), indicating that there are more functioning pancreatic β-cells in rats undergoing this treatment compared to those without treatment.

The limitation of this study lies in inducing type 2 diabetes mellitus (T2DM) using STZ, which is not directly caused by obesity. Additionally, there is a limitation in maintaining obese rats for an extended period while waiting for the onset of DMT2 with all its associated complications.

CONCLUSION

Sleeve gastrectomy combined with pancreatic omentoplasty enhances pancreatic β-cell status by elevating VEGF and PDX1 levels, increasing the Langerhans islet area and pancreatic β-cell count compared to sleeve gastrectomy alone. This research suggests that combining sleeve gastrectomy with pancreatic omentoplasty may offer a potential therapeutic approach for improving pancreatic β-cell function and regeneration, which could have significant implications for treating diabetes in obese humans.

ACKNOWLEDGEMENTS

The authors wish to thank the providers who participated in this study. The authors also thank the research team members for contributing to this study.

Compliance with Ethical Guidance for Animal Study: This animal study was approved by the Ethics Committee, Faculty of Medicine, Universitas Diponegoro. All experimental animals were treated following ARRIVE guidelines and European Union Directive 2010/63/EU for animal experiments.

Ethical permission: Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia ERC letter No. 75/ EC/H/FK-UNDIP/VII/2021.

Conflict of Interest: No conflicts of interest, as stated by authors.

Financial Disclosure / Grant Approval: No funding agency was involved in this research.

Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Mughni A: Conceptualization, methodology, investigation, formal analysis, resources, writing original draft, writing review and editing

Rudiman R: Methodology, investigation, formal analysis, resources, writing the original draft

Pemayun TGD: Investigation, formal analysis,

resources, writing the original draft
Renata B: Investigation, writing the original draft
Mahati E: Investigation, writing the original draft
Hadisaputro S: Investigation, writing original draft
Riwanto I: Writing, review and edit
All named authors take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

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