



Sleeve Gastrectomy and Liver Omentoplasty Can Increased IL-10 and TGF-B Expression on Liver Fibrosis in Obesity

Primadita Purnamasari^{1*}, K. Heri Nugroho², Sigit Adi Prasetyo³, Yan Wisnu Prajoko⁴, Fatmala Haningtyas¹,
Sindu Nugroho Mukti¹, Addy Saputro¹, Abdul Mughni Rozy³

¹Department of Surgery, Faculty of Medicine, Universitas Diponegoro, Dr. Kariadi General Hospital, Semarang, Indonesia; ²Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Dr. Kariadi General Hospital, Semarang, Indonesia; ³Department of Digestive Surgery, Faculty of Medicine, Universitas Diponegoro, Dr. Kariadi General Hospital, Semarang, Indonesia; ⁴Department of Surgical Oncology, Faculty of Medicine, Universitas Diponegoro, Dr. Kariadi General Hospital, Semarang, Indonesia

Abstract

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*Correspondence: Primadita Purnamasari, Department of Surgery, Faculty of Medicine, Universitas Diponegoro/ Dr. Kariadi General Hospital, Semarang, Indonesia. E-mail: primadita.purnamasari@gmail.com

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BACKGROUND: Obesity is a risk factor happening liver fibrosis because it makes presence of oxidative stress and inflammation that has role on pathogenesis and hepatic fibrosis progression. Until this moment, liver disease management still focused for treat disease primary, the most rational management of liver fibrosis is liver transplant, however number success transplant liver lower from on transplant kidneys, only 70–80% of recipients survived for at least 1 year, so that sleeve gastrectomy and liver omentoplasty procedure could become a choice for treating liver fibrosis on obese patients.

AIM: This study aims to investigate correlation between sleeve gastrectomy and omentoplasty on TGF- β and IL-10 in obese rats with liver fibrosis

METHODS: This study used a true experiment *in vivo* design on male Wistar rat (Sprague Dawley) 4–6 weeks of age. Samples were divided into groups that includes normal control group, positive control group, group with sleeve gastrectomy, and group with both liver liver omentoplasty and sleeve gastrectomy. The level of TGF- β and IL-10 will be measured for descriptive and hypothesis analysis.

RESULTS: There is an increased level of IL-10 and TGF- β . Statistical analysis result shows a significant increase of IL-10 and TGF- β expression between normal group and control group with group given treatment sleeve gastrectomy and liver liver omentoplasty ($p < 0.05$).

CONCLUSION: liver Liver omentoplasty and sleeve gastrectomy procedure on obese mice with liver fibrosis exist increases IL-10 expression but could not reduce (TGF- β expression).

Introduction

Accumulation of excessive fat in our body called as obesity. High-incidence of obesity was caused mainly by high-calories, low fiber diet, and lack of physical activities [1]. The World Health Organization stated that around 1 billion people in the world are obese, while data said 300 million people were clinically diagnosed as obesity. This is a risk factor for various metabolic and degenerative diseases such as insulin resistance, diabetes mellitus (DM), hypertension, heart disease, cardiovascular disease, and cancer [2]. Obesity can trigger body having oxidative stress, by increasing the production of pro-oxidants substance. This situation will cause the formation of reactive oxygen species (ROS) so that it can give rise to various other diseases, one of which is liver fibrosis. Inflammatory conditions and the presence of oxidative stress play a role in the pathogenesis and progression of liver fibrosis.

Liver fibrosis is a pathophysiological process, which causes excessive extracellular matrix deposition due to persistent liver damage. Liver fibrosis causes about 1.5 million deaths per year due to end-stage liver cirrhosis and liver cancer. In Indonesia, the problem of liver fibrosis is a health problem that is still rarely realized by the public because it does not show symptoms for a long time. Until now, the management of liver disease is still focused on treating the primary disease; the only rational treatment for liver fibrosis is liver transplantation. Liver transplantation was clearly stated as the sole option of treatment when body having a liver failure [3]. While the success rate data were stated that liver transplantation results are more inferior than kidney transplantation, only 70–80% of recipients survive for at least 1 year.

Based on this, other treatment procedures are needed to increase the effectiveness of the treatment, including sleeve gastrectomy and liver liver omentoplasty. The sleeve gastrectomy procedure is a

procedure performed for laparoscopic weight loss [4]. Compared to gastric bypass, sleeve gastrectomy has a faster and more effective weight loss result [5]. The main effect obtained from the sleeve gastrectomy procedure is a decrease in caloric intake due to a reduction in the gastric surface area for nutrient absorption which will then have an effect on weight loss of 60–70% in the first 12–18 months after the procedure with an average weight loss of 56 kg [6]. In the other hand, omentoplasty was known as filling/cover defect organ procedure. Omentoplasty has been widely used in various surgical procedures because of widely varieties biological function of omentum itself. This study aims to investigate correlation between sleeve gastrectomy and omentoplasty on transforming growth factor beta (TGF- β) and interleukin-10 (IL-10) in obese rats with liver fibrosis.

Methods

Study design and participants

This is an experimental *in vivo* research, post-test only group design. Research and data collection was carried out for 6 months. Obesity rats were treated and observed at the Faculty of Medicine, Gadjah Mada University. PCR was taken at the SCCR Laboratory of Sultan Agung Islamic University. Sprague–Dawley rats aged 4–6 weeks weighing 200–300 g obtained from iRATco Animal Rat Provider. Samples were divided into two control groups and two treatment groups. The sample was randomized using computer software.

Animal treatment and data collection

Animal treatment procedure started with induction of anesthesia with ketamine 10 mg/kgBW and xylazine 1 mg/KgBW followed by decapitation or perfusion and the abdomen was shaved. Then, laparotomy was performed. The procedure was done carefully to avoid accidental penetration into chest cavity.

Sleeve gastrectomy operation procedure starts with rats fasted for 10 h and administered ketamine injection at a dose of 2 mg/kg BW of ketamine \times 70 kg \times 0.018, then asepsis and antisepsis were performed at the operating area as well as an incision on the left subcostal. After that, we had to identify fundus gaster. When identification is complete, the stomach is sutured with polypropylene 3.0 and the abdominal cavity is cleaned with warm 0.9% NaCl. Finally, the surgical wound is closed layer by layer. Meanwhile for liver omentoplasty Surgery Procedure rats fasted for 10 h and administered ketamine injection at a dose of 2 mg/kg BW of ketamine \times 70 kg \times 0.018, then asepsis and antisepsis was performed

at the operating area as well as an incision on the left subcostal. After that, the omentum and pancreas were identified. If identification has been completed, the omentum covering the body of the pancreas is sutured with polypropylene 3.0 and the abdominal cavity is cleaned with warm 0.9% NaCl. Finally, the surgical wound is closed layer by layer and PCR test is done to obtain rRNA concentration measurement.

Data analysis

All collected data were analyzed using SPSS for Windows. Data distribution test was done using Shapiro–Wilk. Non-parametric test was carried out using Kruskal–Wallis and Mann–Whitney test. And the correlation was used Spearman. Ethical Approval was obtained from Ethic Committee of Kariadi General Hospital, Semarang.

Results

Obesity conditions can cause metabolic changes and adiposopathy that can be seen from the increased expression of adiposity which causes inflammation of adipose tissue and macrophage infiltration, which causes a decrease in the expression of the anti-inflammatory cytokine IL-10 and an increase in pro-inflammatory cytokines IL-6, TGF- β , and TNF. IL-10 is a cytokine that produces an inhibitory factor for T lymphocytes produced by T helper 2 (Th2) cells and γ interferon synthesis in Th1 cell clones, a study has shown that long-term IL-10 therapy reduces liver inflammation and fibrosis.⁷ Transforming growth factor (TGF)- β is a multipotent cytokine secreted by various cells in the body. The cytokine TGF- β is one of the cytokines that play a role in the process of fibrosis because it can activate interstitial fibroblasts, induce apoptosis (which causes renal intrinsic cells to be lost, replaced by fibrotic tissue), and differentiation of tubular cells into myofibroblasts.

In this study, the sample in the form of Wistar rats was divided into two control groups and two treatment groups. Samples in treatment group will undergo a predetermined diet for 4 weeks and then administer carbon tetrachloride (CCl₄-) injection to induce a liver fibrosis model in the sample. After 10 days, the samples were taken and analyzed. The results of statistical analysis showed that there was a significant difference in IL-10 expression between the normal group and the control group and the sample group that was treated with sleeve gastrectomy and liver omentoplasty and between the control group was significant to the sample group that was treated with sleeve gastrectomy and liver omentoplasty ($p < 0.05$) (Figure 1). In addition, there were also significant differences in TGF- β

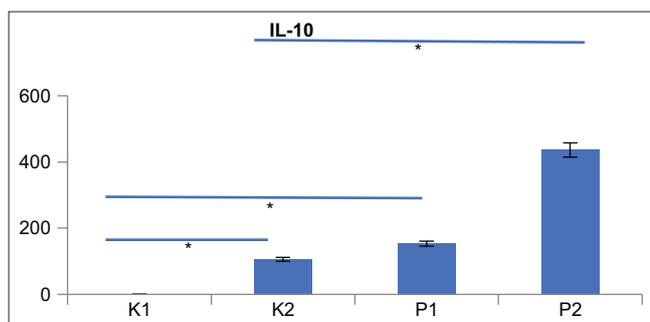


Figure 1: IL-10 expression level. K1: Negative control group, K2: Positive control group, P1: Sleeve gastrectomy group, P2: Sleeve gastrectomy and liver omentoplasty group

expression, between the normal sample group and the control group and the sample group that was treated with sleeve gastrectomy and liver omentoplasty. Significant difference in TGF- β expression also seen between the sample group that was only treated with sleeve gastrectomy and the sample group that was treated with sleeve gastrectomy and liver omentoplasty and between the control group and the sample group that was treated with sleeve gastrectomy and liver omentoplasty ($p < 0.05$) (Figure 2). Significantly difference was found in negative and control group with the group treated with sleeve gastrectomy and liver omentoplasty, which indicates that the combination of sleeve gastrectomy and liver omentoplasty increased the expression of IL-10 and TGF- β .

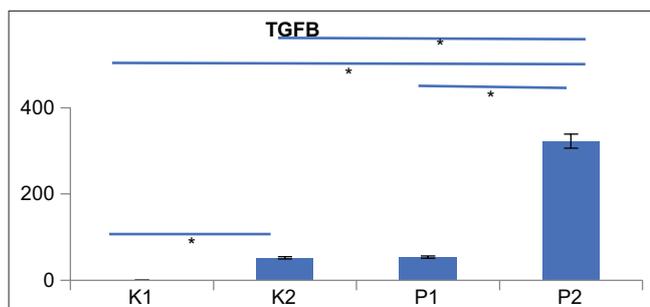


Figure 2: TGF- β expression level. K1: Negative control group, K2: Positive control group, P1: Sleeve gastrectomy group, P2: Sleeve gastrectomy and liver omentoplasty group

Discussion

Significant differences between the sleeve gastrectomy and liver omentoplasty treatment groups with other groups found in this study showed increased levels of TGF- β after the procedure treatment. This is not in line with previous studies, where almost all of them reported a decrease in TGF- β levels. In the study by Salman *et al.* (2020), sleeve gastrectomy procedure can reduce body weight in pediatric patients with obesity and NASH-associated liver fibrosis [7]. Obesity conditions can increase the release of TGF- β by adipose tissue, overcoming obesity conditions can

reduce the risk of inflammation in adipose tissue so that the release of pro-inflammatory agents can be overcome. Therefore, sleeve gastrectomy and liver omentoplasty procedures are expected to reduce the release of TGF- β to improve liver recovery.

The elevated levels of TGF- β in this study may be due to the role of TGF- β which can contribute to both damage and healing of the liver. TGF- β plays a role in inducing and regulating apoptosis of hepatocyte cells. The study by Yang *et al.* investigated the implantation of liver progenitor cells treated with TGF- β . Yang *et al.* reported that TGF- β acts as a knife with two sharp edges in a fibrotic process. TGF- β is known to regulate development, regeneration differentiation, fibrogenesis, tumorigenesis, and metastasis. The study found that TGF- β can result in two opposing regulations against the same liver progenitor cells in the progression pathway of chronic liver disease [8]. This function of TGF- β may be one of the possible reasons for its high expression levels after sleeve gastrectomy and liver omentoplasty procedures, which use the omentum as a progenitor that differentiates to promote healing.

The activation of TGF- β which makes its levels increase in the circulation can be influenced by several factors, such as proteases, integrins, pH, and reactive oxygen species. Plasmin and several matrix metalloproteinases have an important role in promoting tumor invasion and tissue remodeling by inducing proteolysis, resulting in the release of TGF- β to its receptors. pH also plays an important role, where acidic conditions can denature Latency-Associated Peptide (LAP) which was found to activate TGF- β . ROS that generate hydroxyl radicals are also known to cause TGF- β activation through modification of the LAP structure [9]. In addition, the study found that the expression of TGF- β was also able to trigger an increase in the expression of PDGF, a growth factor that plays a role in liver fibrosis. This shows that TGF- β can have a good impact on the process of liver fibrosis disease progression and can play a role in the healing process through activation and differentiation of progenitor cells in the liver [10].

In this study, the increase in IL-10 after sleeve gastrectomy and liver omentoplasty was a physiological response of the body to liver fibrosis conditions. This finding is in line with previous studies which found that there was a significant increase in IL-10 levels in CCl₄-induced mice. Adipose tissue is thought to be the source of upregulated IL-10 [10], [11]. It has been showed that this result was demonstrated in the same way as previous study. IL-10 and IL-10 receptor expression was mainly in adipose tissue, as anti-inflammatory cytokine, it will help to reduce and prevent further liver damage. This study showed the importance of IL-10 in prevention of recurrent liver fibrosis [12].

The high level of IL-10 expression is also in accordance with what was reported by Ekasaputra *et al.* (2022) which showed that sleeve gastrectomy

procedure can inhibit inflammatory mediators such as IL-6 through the increase of IL-10 cytokines [11]. The sleeve gastrectomy procedure will cause changes in the body's metabolic parameters such as an increase in the hormone Glucagon Like Peptide 1 (GLP-1) which is a hormone secreted by enteroendocrine cells in the intestine, this hormone functions to stimulate β cell growth and reduce apoptosis. GLP-1 has alternative anti-inflammatory function due to the involvement in intestinal intraepithelial lymphocytes [13].

Conclusion

Liver omentoplasty and sleeve gastrectomy procedures performed on obese rats with liver fibrosis did not reduce the expression value of transforming growth factor beta (TGF- β). Meanwhile, the same procedures performed on obese rats with liver fibrosis can increase the expression value of interleukin-10 (IL-10).

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