Role of liver damage on glucose metabolism in a lipopolysaccharide-induced mouse model

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ABSTRACT

Introduction: The multi-organ damage brought on by sepsis’ bacterial infection process makes it a significant cause of death in hospitals. The inflammatory process is triggered by LPS, which is produced by bacterial infection. LPS protects against liver damage, however its exact mechanism is still unknown. The purpose of this investigation is to quantify the extent of liver damage and insulin receptor expression in LPS-induced animal models.

Methods: Eight-week-old male mice were separated into three groups: control group (Group 1), LPS injection group (10 mg/Kg body weight for 4 hours), and LPS injection group (10mg/Kg body weight for 8 hours). Blood sugar and weight are measured as part of the examination of metabolism. To check for liver damage, histology was done.

Results: In comparison to the control group, long-term LPS injection significantly decreased body weight and blood sugar levels (P < 0.05). Based on the high liver damage score in groups 2 and 3 compared to the control group (P < 0.05), this LPS induction also caused harm to the liver's ability to operate.

Conclusion: As a consequence of our research, we may infer that LPS injection damages the liver and produces metabolic abnormalities that are characterized by weight loss and low blood glucose levels.

Keywords: LPS, Liver Injury, Oxidative stress.


INTRODUCTION

Gram-negative bacterial infections are the primary cause of sepsis, a clinical state involving an inflammatory response that has a high fatality rate. Lipopolysaccharide (LPS), a crucial component of Gram-negative bacteria’s cell walls, has been linked to a number of studies showing that it can harm tissues and organs such as the heart, kidneys, and liver by causing the release of pro-inflammatory cytokines and reactive oxygen species (ROS). Previous studies have revealed that LPS has a significant impact on the onset of liver damage. Elevated plasma levels of LPS are linked to cirrhosis and liver fibrosis, according to clinical and animal studies. Due to the depletion of intracellular antioxidants, which results in lipid peroxidation and oxidative damage, inflammatory mediators like TNF-α and IL-6 are triggered by LPS currents and can harm the liver.

LPS-induced inflammation not only damages the liver but also interferes with other bodily processes, including the microbiota in the colon, which regulate metabolism. The gut microbiota and pathogenic gastrointestinal processes have recently been linked. Insulin resistance is thought to be exacerbated by Gram-negative bacteria that produce lipopolysaccharides (LPS, also known as endotoxins). According to the notion, a high-fat diet can change intestinal flora and intestinal wall permeability, which increases the formation of enterobacteria and facilitates the translocation of LPS into the systemic circulation. In obese and T2DM experimental mice, this condition is connected to the progression of insulin resistance. Additionally, earlier research has demonstrated an increase in plasma LPS concentrations in a number of groups of obese and T2DM participants, and LPS induction in healthy conditions can result in a greater rise in insulin resistance. In the systemic inflammatory process that results from obesity, insulin resistance, and T2DM, rising LPS concentrations are therefore crucial.

In addition to causing greater systemic inflammation, liver damage is a frequent side effect of insulin resistance and T2DM. Additionally, new research has demonstrated the role that adipokines play in the liver’s direct and local inflammatory response. Consequently, the development of insulin resistance is influenced by liver injury. It is yet unknown how sepsis causes insulin resistance and liver damage, though. Therefore, the purpose of this study is to quantify the extent of liver injury and insulin receptor expression in LPS-induced animal models.

METHODS

Study Design
This type of research is experimental using animals in vivo experiments. Experimental research is a research with intervene or treat a variable. Eight-week-old male Mus musculus of weights between 20 to 30 g, were obtained from PUSVEPMA laboratory in Surabaya. The animals were acclimatized for one week at room temperature (25–30 °C), had access to feed and water ad libitum under a 12-h light/12-h dark. After one
week, mice were injected with LPS 10 mg/kg body weight for 4 hours and 8 hours. Lipopolysaccharide (LPS) was purchased from Sigma (St.Louis, USA).

**Measurement of Blood Glucose Levels and Body Weight**
The blood glucose level was observed using a digital blood glucose level and Glucostick (Gluco-Dr). Experimental animal body weight was measured using a digital scale (Weston).

**Historical and Immunohistochemical Analyses**
On the 14th day, the animals were sacrificed, and the complete livers were taken out, preserved in 10% formalin solution, and processed using the paraffin method. Hematoxylin and eosin (H&E) was used to stain sections of 5 μm thickness for histological analysis.

**Statistical Analysis**
All findings are shown as mean SEM. With an unpaired Student's t-test, parameters were compared between the two groups. Tukey's post hoc test was used to compare dose-response curves between groups after two-factor repeated measures ANOVA was used to compare the curves. Significant results were defined as p < 0.05.

**RESULTS**

**Changes in Body Weight and Blood Sugar Levels After LPS-induction**
Body weight and blood sugar levels changed after intraperitoneal administration of LPS at a dose of 10 mg/kg. In this study, there was no significant difference in body weight in the LPS injection group at the longer time of 8 hours (group 3), but there was a significant difference in body weight change in the LPS injection group within 4 hours (group 2), which was significant compared to the control group (group 1) (p < 0.05). Figure 1 (A) demonstrates that there was a significant difference between groups 2 and 3 (p < 0.05). It is well recognized that LPS injection can result in sepsis, which in turn affects liver metabolism. The results of this study showed that LPS injection caused a significant decrease in blood sugar levels when compared to the control group (p < 0.01) in group 2 and group 3 (figure 1B).

**Figure 1.** Changes in body weight and blood sugar levels after LPS-induction.

**DISCUSSION**
LPS administration's impact on human sample FGF21 responses was previously studied. According to certain academic research, inflammatory pathways control FGF21 for longer than 48 hours. LPS and glucose are known to suppress FGF21 at various times. In addition, FGF21 gradually increased following LPS induction. Previous research have also shown that insulin-resistant diseases such as poor glucose tolerance, obesity, and type 2 diabetes mellitus patients have higher plasma concentrations of FGF21. Both hepatic and peripheral insulin resistance are directly correlated with FGF21 levels. Plasma levels of FGF21 are likely to rise compensatorily as a result of its role in suppressing lipolysis in adipose tissue through inhibition of liver gluconeogenesis by affecting carnitine-
palmitoil-transferase-1 (CPT1 and CPT1), adenosine-monophosphate-activated protein kinase-1 (AMPK1), carnitine-palmitol-transferase.11–13 Recent research has also revealed that adiponectin and other insulin-sensitizing hormones, specifically, appear to trigger the liver’s production of FGF21. To increase the severity of the liver injury, a high dose of LPS (5 mg/kg) was administered. LPS injection was able to elevate serum levels and stimulate the liver’s synthesis of FGF21.14–16

In this study, we investigated the effect of LPS induction on liver injury. The findings show that LPS induction induces liver lobe injury, cell infiltration, bleeding, and hepatocyte necrosis, as well as a brief decrease in blood glucose levels. The main fatal cause is sepsis brought on by an infection. Sepsis-related deaths often result from liver damage. A tiny amount of LPS has been shown to produce severe liver damage in mice, and it has been discovered to play a significant role in the pathogenesis of infection1. By causing excessive inflammation, increased oxidative stress, and mitochondrial damage, LPS damages tissue.17 When LPS binds to the Toll-like receptor 4 (TLR-4) on Kupffer cells, these cells get activated and release excessive amounts of pro-inflammatory cytokines and ROS, which causes liver cells to die or undergo necrosis. Therefore, inflammation and oxidative stress play a role in the liver damage caused by LPS.18

CONCLUSION

Our findings indicate that LPS injection damages the liver and induces metabolic abnormalities that are manifested by low blood sugar and weight loss. To further understand the many parameters that influence the severity of liver damage and insulin receptor expression in LPS-induced animal models, additional research is required.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contribution

All authors similarly contribute to the think about from the investigate concepts, information acquisitions, information investigation, factual investigations, changing the paper, until detailing the consider comes about through publication.

Ethical Consideration

Ethical approval was obtained from The Research Ethics Committee of Universitas Nahdlatul Ulama Surabaya (No.49/EC-KEP-UNUSA//I/2021).

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