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Research Article
High Fiber Diet Reduces Gene Expression and Level of IL-1β in Hypertriglyceridemia Rats

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Abstract

Background and Objective: High fat and fructose diet causes hypertriglyceridemia that induce production of proinflammatory interleukin Iβ (IL-Iβ). Expression of IL-Iβ can be suppressed by short chain fatty acids (SCFA).This study aimed to determine the effects of high fiber diet on the level and expression of IL-1β in high fat and fructose diet model of Wistar rats. **Materials and Methods:** Twenty-five Wistar rats divided into 5 groups: Normal control (N), hypertriglyceridemia control (TC), hypertriglyceridemia with 1.04 g rat^{-1} day^{-1} of fiber (T1); hypertriglyceridemia with 2.07 g rat^{-1} day^{-1} of fiber (T2) and hypertriglyceridemia with 3.11 g rat^{-1} day^{-1} of fiber (T3). Triglyceride levels were measured using colorimetric method, whereas IL-1β levels were measured using ELISA method. All biochemical analysis was performed twice, before and after treatment. IL-1β gene expression in white adipose tissue was measured by q-PCR method at the end of the study. **Results:** Triglyceride levels in treatment groups were lower compared to hypertriglyceridemia control group. Gene expression and levels of IL-1β at treated groups, receiving high fiber diet, were lower compared to the hypertriglyceridemia control group. **Conclusion:** High fiber diet could suppress the expression of IL-1β in white adipose tissues and could reduce the level of IL-1β in rats.

Key words: High fiber diet, hypertriglyceridemia, gene expression, inflammation, IL-1β

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

High fat and fructose diet increase the secretion of very low-density lipoprotein (VLDL), causing hypercholesterolemia and hypertriglyceridemia, which are symptoms of a lipid metabolism disorder called hyperlipidemia[1]. The mechanism of hyperlipidemia starts with the liver secreting VLDL which transports triglyceride to peripheral tissues[2]. Triglyceride is hydrolyzed by lipase lipoprotein, producing free fatty acids (FFA) to be stored in tissues such as healthy muscles and skeletal muscles[3]. The higher the triglyceride level, the higher the FFA level, which can induce an inflammatory response[4]. FFA bind to Toll-like receptor 2 (TLR 2) and Toll-like receptor4 (TLR 4) which induce nuclear factor-kappa β (NFκβ) to secrete proinflammatory cytokines such as IL-1β[5]. FFA also stimulates the activation of NOD-like receptor protein3 (NLRP3) which will activate Caspase-1[6], then Caspase-1 will turn pro IL-1β into IL-1β[7].

IL-1β is a proinflammatory cytokine that has a broad spectrum of immunological activity[8]. IL-1β production is regulated by 2 mechanisms i.e., TLR activation and activation by NLRP3 inflammasome[9]. The first mechanism through activated TLR, especially TLR 2 and TLR 4, will trigger the activation of NFκβ, then NFκβ secretes pro-inflammatory cytokine such as IL-1β[10]. The second mechanism through NLRP3 inflammasome complex produces pro-Caspase 1 and is activated into Caspase-1[11]. Caspase-1 activates pro-IL-1β into active and mature IL-1β. The expression of geneIL-1β is induced by NFκβ transcription factor[12]. NFκβ and production of inflammatory cytokines such as IL-1β can be suppressed by short-chain fatty acids (SCFA)[13].

SCFA are formed when food fiber is fermented by anaerobic bacteria in the large intestines[14]. SCFA affects 3 signaling pathways, which are G-protein receptor (GPR) activation, histone deacetylase (HDAC) inhibition[15] and histone acetyltransferase (HAT) activation[16]. Activation of the GPR pathway, especially GPR41 and GPR43, is important for the expression of inflammatory mediators such as IL-1β[13]. The main SCFAs produced in human intestines are butyrate, propionate and acetate[17]. Butyrate can inhibit the activation of NF-κB transcription factor[15]. Butyrate and propionate can suppress the secretion of IL-1β through HDAC inhibition mechanisms[18]. The present study was conducted to determine the effect of high fiber diet on the level and expression of IL-1β in high fat and fructose diet of Wistar rats.

MATERIALS AND METHODS

Animals: A total 25 male Wistar rats that obtained from BioFarma, aged 8 weeks and weighed 150-200 g were used in this study. The rats were housed in individual caged and maintained in standard condition (22-25°C room temperature and 12:12-h light/dark cycle). They were adapted for 7 days with standard diet (AIN 93 M). This study was approved by Ethics Committee of the Integrated Research and Testing Laboratory, Universitas Gadjah Mada (Approval No.: 00065/04/LPPT//2017).

Experimental study: The rats were divided into 5 groups after adaptation, normal control group (N) was fed standard diet (AIN-93 M), while 4 groups were fed high fat and fructose diet for 7 weeks. The standard diet (AIN-93 M) was made with substitution of L-Cystine by DL-methionine and choline bitartrate by choline chloride. The high fat and fructose diet were prepared according to the methods described by Ble-Castillo *et al.*[19] and Sasidharan *et al.*[20], by replacing sucrose into fructose and trans-fat into corn starch. The composition of standard diet consists of 61.94% corn starch, 14% casein, 10% sucrose, 4% corn oil, 5% cellulose, 3.5% mineral mixture, mixture of vitamin 1%, DL-methionine 0.3%, choline chloride 0.25% and tetra butil hydroquinone 0.008%. While treatment diet for T1, T2 and T3 refers to a standard diet with substitution of corn starch using sweet potatoes and pumpkin with a total fiber of 6.88, 13.77 and 20.65 g, respectively per 100 g of diet.

Rats with >70.79 mg dL^{-1} plasma triglyceride levels were considered as hypertriglyceridemia conditions[21]. After 7 weeks of induction, one group of rats received no high-fiber diet and served as hypertriglyceridemia control group (TC), while 3 other groups received high-fiber diet in different dosage i.e. 1.04 g rat^{-1} day^{-1} (T1), 2.07 g rat^{-1} day^{-1} (T2) and 3.11 g rat^{-1} day^{-1} (T3). The high-fiber diet was given for 6 weeks. The blood sample was drawn from medial canthus sinus orbitalis under anesthesia condition. The triglyceride and IL-1β levels were determined twice, before and after administration high-fiber diet. At the end of the study, the white adipose tissues were taken to analyzed IL-1β gene expression. Collecting of the samples were done after overnight fast.

Biochemical analysis: The triglyceride levels were analyzed using colorimetric method (DiaSys, Holzheim, Germany). The IL-1β levels were analyzed using Enzyme-linked immunosorbent assay (ELISA) method (Fine Test, Wuhan, China).

Table 1: Primer sequence

Genes	Primer
IL-1β (rat)	Forward 5′-TTCCCTGGGAGAGAAGCTGA-3′
	Reverse 5′-ATGGCCTTGTAGACACCTTTGT-3′
Beta actin	Forward 5′-ACGGTCAGGTCATCACTATCG-3′
	Reverse 5′-AGCCACCAATCCACACAGA-3′

Isolation of RNA and quantitative polymerase chain reaction (q-PCR): Total RNA was extracted from frozen adipose tissue using TRIzol reagent (Invitrogen, USA). The reverse transcription of 1 µg of total RNA was done according to protocol Applied Bio-systems™ High-Capacity cDNA Reverse Transcription Kit (Fisher Scientific, USA). The results were quantified relative to β-actin based on $2^{-\Delta\Delta Ct}$ method[22]. The primer sequence for IL-1β and beta actin is presented in Table 1.

Statistical analysis: Data were presented as Mean±standard deviation (SD). Paired t test was used to analyze triglyceride and IL-1β levels before and after intervention. Differences were considered statistically significant at $p<0.05$.

RESULTS

Triglyceride levels: The analysis results of triglyceride levels before and after intervention were shown in Fig. 1. The rats in TC group have significantly increased triglyceride levels after induction of high fat and fructose diet. Whereas after receiving the high fiber diet, the hypertriglyceridemia rats had lower triglyceride levels ($p<0.05$). Although, all three doses of fiber in diet decreased significantly but the decreasing of triglyceride in 2nd and 3rd doses were almost same.

IL-1β levels: Figure 2 shows the levels of serum IL-1β before and after intervention of high dietary fiber. Induction high fat and fructose diet can significantly induce inflammation that characterized by high IL-1β levels (TC, T1, T2, T3) before intervention ($p<0.05$), while intervention with dietary fiber could reduce the IL-1β levels. The best effects of dietary fiber on IL-1β levels were found in administration of 2.07 g rat^{-1} day^{-1} (T2).

Expression of IL-1β in white adipose tissue: Expressions of IL-1β in white adipose tissues are shown in Fig. 3. The expressions of IL-1β in the T1 and T2 groups were lower than that of the TC group. There were no significantly different expressions of IL-1β in white adipose tissues in the TC group with those of T3 group.

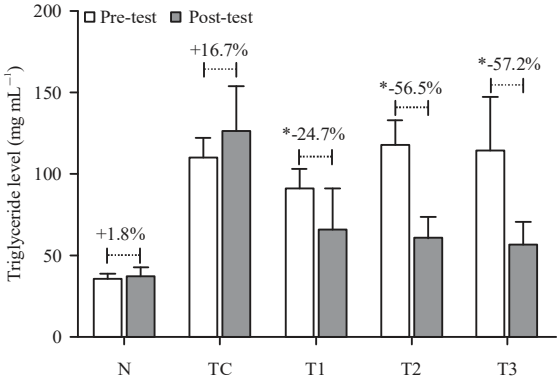

Fig. 1: The levels of serum triglyceride in rats before and after intervention

N: Normal control, TC: Hypertriglyceridemia control, T1: Hypertriglyceridemia with 1.04 g rat^{-1} day^{-1} of fiber, T2: Hypertriglyceridemia with 2.07 g rat^{-1} day^{-1} of fiber and T3: Hypertriglyceridemia with 3.11 g rat^{-1} day^{-1} of fiber (T3). Data are presented as Mean±standard deviation (SD). *Mark indicate $p<0.05$ according to paired t-test

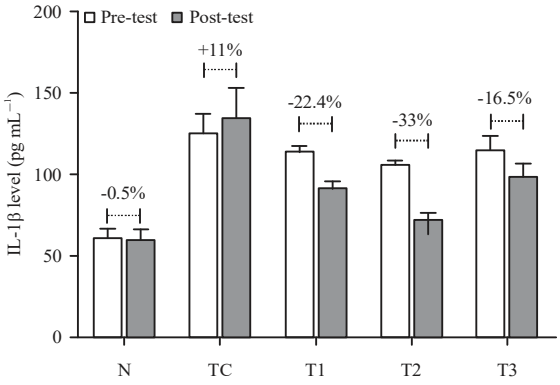

Fig. 2: The levels of serum IL-1β in adipose tissue rats before and after intervention

N: Normal control, TC: Hypertriglyceridemia control, T1: Hypertriglyceridemia with 1.04 g rat^{-1} day^{-1} of fiber, T2: Hypertriglyceridemia with 2.07 g rat^{-1} day^{-1} of fiber and T3: Hypertriglyceridemia with 3.11 g rat^{-1} day^{-1} of fiber (T3). Data are presented as Mean±standard deviation (SD).

DISCUSSION

In this study, the rats received high-fat and fructose diet showed hypertriglyceridemia seen by inducing inflammation factor indicated by increased IL-1β in TC, T1, T2, T3 groups (Fig. 1). According to Saponaro *et al.*[23], high fat and/or carbohydrate intakes stimulates lipogenesis associated with inflammation. Mild to moderate hypertriglyceridemia related to low-grade inflammation. In mild to moderate

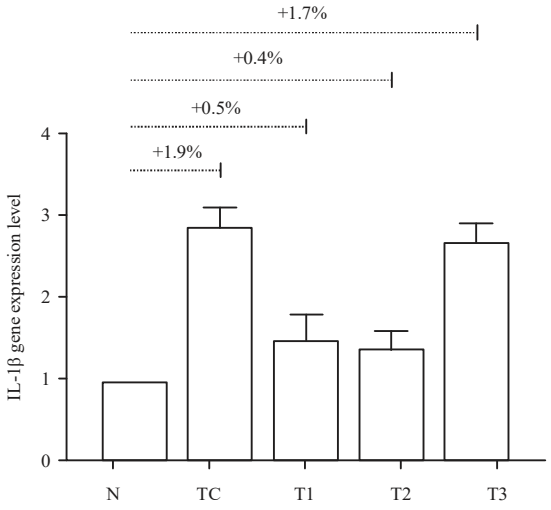

Fig. 3: Expression of IL-1β in white adipose tissues

N: Normal control, TC: Hypertriglyceridemia control, T1: Hypertriglyceridemia with 1.04 g rat^{-1} day^{-1} of fiber, T2: Hypertriglyceridemia with 2.07 g rat^{-1} day^{-1} of fiber and T3: Hypertriglyceridemia with 3.11 g rat^{-1} day^{-1} of fiber (T3). Data are presented as Mean±standard deviation (SD)

hypertriglyceridemia, lipoprotein lipase hydrolyzes triglyceride into free fatty acids and monoacylglycerols caused low-grade inflammation[24]. Triglycerides are the main component of triglyceride-rich lipoproteins including, chylomicrons and VLDL, which were involved in inflammation through direct and indirect pathways. In other hand, high-fat diet intake could alter microbial composition in the intestine by increasing the ratio of *Firmicutes* to *Bacteroidetes* that is associated with increased gut permeability and enhanced circulating lipopolysaccharides levels, which could induce systemic in ammation[25].

This study showed the administration of high-fiber diet could reduce the levels of triglyceride and IL-1β. Hannon *et al.*[26] reported that total and soluble dietary fiber was an independent factor in triglyceride levels and its relationship was inversely related in overweight and obese individuals. Decreased triglyceride in rats with fiber 2.07 g rat^{-1} day^{-1} (T2) or 3.11 g rat^{-1} day^{-1} (T3) seems similar but the decreased IL-1β levels in rats with fiber 2.07 g rat^{-1} day^{-1} (T2) were greater than those in rats with 3.11 g rat^{-1} day^{-1} (T3). The same results were found in IL-1β gene expression. The IL-1β gene expression in rats with fiber 2.07 g rat^{-1} day^{-1} (T2) were lower than those in rats with 3.11 g rat^{-1} day^{-1} (T3). It showed that the levels of IL-1β depend on the IL-1β gene expression. Interleukin 1 (IL-l) is a key mediator of inflammation. Fang *et al.*[27] reported that dietary fiber significantly increases anti-inflammatory mRNA levels and decreases pro-inflammatory cytokine mRNA levels in the jejunum, liver and spleen. Different fibers have different effects on immune function in the jejunum, liver and spleen through the level of expression of anti-inflammatory and pro-inflammatory cytokine genes.

Decreased IL-1β levels after giving high-fiber diet in line with the previous study that reported high-fiber diet could reduce inflammatory responses characterized by lower IL-1β[28]. This effect is suspected due to SCFA contents, especially butyrate, one of fermentation results from food fiber, suppressing production of inflammatory mediators such as IL-1β[29], through reducing HDAC activity[30]. HDAC and HAT control the level of protein acetylation. Inhibition of HDAC activity will increase histone and non-histone protein acetylation, including NFκB, preventing the activation of NFκB[31]. Prevention of NFκB activation also plays a role in preventing the release of pro-inflammatory cytokines such as IL-1β[32].

The highest reduction of IL-1β level in rats given dietary fiber was found in the rats receiving 2.07 g fiber rat^{-1} day^{-1}, while other rats with 1.04 or 3.11 g fiber rat^{-1} day^{-1} lower than that of the rats with 2.07 g fiber rat^{-1} day^{-1}. It showed that production of SCFAs by colonic bacteria depends on the balance between bacteria and their food. In low fiber, bacteria produce small amount of SCFAs but in high fiber, the fiber may disturb the bacteria activity. Therefore, increase of dietary fiber dosage did not always increase ability to reduce IL-1β level, dependon the number of microflorae in the colon. SCFAs work with cytokines in leukocytes and endothelial cells through two mechanisms, i.e., GPR activation and HDAC inhibition[29]. SCFA regulates cytokine production, including IL-1β[13].

In this study, the expression of IL-1β gene in white adipose tissue correlated with IL-1β levels that showed by lowest one in the rats received 2.07 g fiber rat^{-1} day^{-1}, although the gene expression is almost similar with rats received 1.04 g fiber rat^{-1} day^{-1}. The expression of gene IL-1β induced by NFκβ suspected from the transcription factor[33]. NFκβ transcription factor can be induced by complex of FFA with TLR 2 and TLR 4[5]. Therefore, in the TC group, the gene expression of IL-1β was highest than others. FFAs bind to their receptors, i.e. TLR2 and TLR4, increasing degradation of IKKβ and causes translocation of NFκβ to the cell nucleus, which may trigger expression of proinflammatory cytokine, including IL-1β[34].

NFκβ and the production of inflammatory cytokines can be suppressed by SCFA[13]. SCFA are formed when dietary fiber is fermented by anaerobic bacteria in the large intestines[14]. SCFA affects 3 signaling pathways, which are

G-protein receptor (GPR) activation, histone deacetylase (HDAC) inhibition[15] and histone acetyltransferase (HAT) activation[16]. Activation of the GPR pathway, especially GPR41 and GPR43, is important for the expression of inflammatory mediators such as IL-1β[13]. The main SCFAs produced in human intestines are butyrate, propionate and acetate[17]. Butyrate can inhibit the activation of NF-κB transcription factor[35]. Butyrate and propionate can suppress the secretion of IL-1β through HDAC inhibition mechanisms[18].

CONCLUSION

Consumption of2.07 g fiber day^{-1} could suppress the expression of IL-1β in white adipose tissues and reduce the level of IL-1β in hypertriglyceridemia rats, induced by high fat and fructose diet.

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