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High Fiber Diets Enhance *IL-10* Gene Expression and Itslevelin Hyperlipidemic Rats Model

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Abstract

Hyperlipidemia induces inflammation by increasing proinflammatory cytokines and reducing anti-inflammatory cytokines. Short chain fatty acids from fiber fermented by intestinal bacteria can reduce inflammation. The aim of this study was to evaluate the benefits of high fiber diet on *IL-10* gene expression and its levels in white adipose tissue in rats with high fat and fructose diet.

High fructose and trans-fat were used to induce hyperlipidemia, while intervention diet for treatment 1 (HL1), treatment 2 (HL2), and treatment 3 (HL3) contain a total fiber of 6.88%, 13.77% and 20.65%, respectively. Serum *IL-10* level was measured using ELISA method before and after intervention, and *IL-10* gene expression was analyzed using quantitative PCR (qPCR) after intervention.

Results: High trans-fat and fructose diet decrease *IL-10* levels, while high-fiber diet can significantly increase the gene expression and levels of *IL-10* in hypertriglyceridemia rats ($p<0.05$). The increased *IL-10* levels was 58.36 pg/mL, 55.86 pg/mL, 76.70 pg/mL respectively within diet containing fiber for 6.88 %, 13.77 %, and 20.65%. However, only diet with 20.65% fiber could significantly increase *IL-10* gene expression (1.26 + 0.54 become 2.74. + 0.22).

Conclusion: High fiber diet could decrease inflammation through increase the gene expression and levels of *IL-10*.

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Introduction

It has been reported that high fructose and saturated fatty acid-diet increase the level of plasma triglyceride and cholesterol in the rats.

High-fructose and/or high-fat diet decrease TG clearance, therefore induce hypertriglyceridemia.[1] In the circulation, the triglycerides carried in chylomicrons are lipolyzed by lipoprotein lipase

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in the capillary bed of tissues using fatty acids for energy (i.e.skeletal muscle and heart) or storage (i.e.adipose tissue). The fatty acids storage will cause adipose tissue expansion and an increase in fatty acid release into the circulation,[2] and activate inflammatory pathways.[3,4]

Free fatty acids could act as signal molecule activating nuclear factor kappa B (NFκB), an important transcription factor in the inflammatory response.[5,4] In this condition, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and plasminogen activator inhibitor-1 (PAI-1) will increase, whereas the anti-inflammatory cytokines such as *IL-10* will decrease.[6,7] Reduction of *IL-10* expression will increase the severity of inflammation due to the function of this cytokine to inhibit the pro-inflammatory effect.[8,9]

Interleukin-10 is a pleiotropic cytokine mainly produced and secreted by macrophages (M2).[10,11] This cytokine has immunosuppressive roles which inhibits the expression of inflammatory genes.[12] The mechanism of action for *IL-10* is by inhibiting the activation of NFκB through the kB-inhibitor (IkB) which induces translocation p50 thereby inhibiting the translocation of the heterodimer p65/p50.[13] Enhancement of *IL-10* expression in an inflammatory state will reduce pro-inflammatory cytokines and reduce the negative effects of inflammation.[11]

Some studies reported that short chain fatty acid (SCFA) can regulate the production of inflammatory mediators through macrophages.[14,15] The SCFA, mainly acetate, propionate, and butyrate could be produced by colonic bacteria as a result of dietary fiber fermentation. Dietary fiber is an undigested carbohydrate that are resistant to gastrointestinal enzymes but could be fermented by colonic bacteria.[16] Propionate acid plays an important role in inhibiting TNF-α and IL-6 secretion and increasing pro-inflammatory cytokines secretion (IL-4 and *IL-10*).[17] Danuyanti *et al.,*[18] reported that high fiber diet decrease TNF-α and IL-6 levels that may be related with suppression of toll-like receptor 4 (TLR4) and NFκB gene expression in hypertriglyceridemia rats. In the present study, we evaluate the benefits of diet with high fiber on gene expression and levels of *IL-10* cytokine in white adipose tissue in rats with high fat and fructose diet.

Material and Methods

This study was done after approvement from Ethical Committee of Integrated Research and Testing Laboratory, University of Gadjah Mada (Approval Number: 00065/04/LPPT//2017). Twenty-five (25) male Wistar rats, aged 8 weeks, body weight 180-200 g were divided into 5 groups: 1) normal control rats (N); 2) hyperlipidemia control rats (HL); 3) hyperlipidemia rats with fiber 1.04 g/rat/day (HL1); 4) hyperlipidemia rats with fiber 2.07 g/rat/day (HL2), and 5) hyperlipidemia rats with fiber 3.11 g/rat/day (HL3). The condition of hyperlipidemia was carried out using a diet high in fat and fructose for 7 weeks, and they were considered hyperlipidemia, if their plasma triglyceride levels were > 70.79 mg / dL.[19] The blood samples used to analysis triglyceride levels were collected from the medial canthus sinus orbitalis from rats fasting for 10 hours into EDTA tube, and then centrifuge at 3000 rpm for 15 minutes. Diet high in fat and fructose were made by replacing the same weight of fructose for sucrose, and trans-fat for corn starch.[20,21]

The rats were individually kept in cages and maintained under standard conditions (12:12-h light/dark cycle and 22-25°C room temperatures). Acclimatization of the rats was done for 7 days using AIN-93M formulation with modification (L-cystine was substituted by DL-methionine and choline bitartrate by choline chloride) and water ad libitum.[22] The normal diet composition 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 tetrabutilhydroquinone 0.008%. While the treatment diet for T1, T2, and T3 refers to a normal diet with substitution of corn starch using sweet potatoes and pumpkin with a total fiber of 6.88 g, 13.77 g and 20.65 g, respectively per 100 g of diet. The diet fiber content was examined by the Center for Food and Nutrition Studies, University of Gadjah Mada.

Before and after intervention, blood samples were collected from the medial canthus sinus orbitalis for serum *IL-10* analysis using ELISA method (FineTest, Wuhan, China) and used as manufacturer's protocol.[23] *IL-10* were calculated based on a standard curve and the ELISA assay was performed

duplicately. Range detection 31.25-2000pg/mL, the inter-assay: CV<10%, and the intra-assay: CV<8%.

The white adipose tissue samples were collected from the retroperitoneal area for *IL-10* gene expression analysis by qPCR. Total RNA was extracted using TRIzol reagent (Invitrogen, USA), according to manufacturer's protocol. Reverse transcription of 1 µg RNA was done based on Revert Aid First Strand cDNA Synthesis Kit (Thermo Scientific, USA). The qPCR assay used SsoFast EvaGreen Supermix (Bio-rad, United Kingdom) with total reaction for qPCR was 10 µL. The qPCR analysis was done using Bio Rad CFX96 Real-Time PCR detection. The conditions of qPCR were 95oC for 10 minutes for early denaturation, followed by 40 cycles of 95oC for 15 sec, 57oC for 1 minute and 72oC for 45 sec.

The results were normalized to β-actin housekeeping gene, and relative gene quantification was performed by using the $2^{-\Delta\Delta Cq}$ method.[24] The specific primer sequences for *IL-10* (purchased from Integrated DNA Technologies, Inc, Singapore) were Forward 5'-TTCCCTGGGAGAGAAGCTGA-3', and Reverse 5'-ATGGCCTTGTAGACACCTTTGT-3',[25] while it for β-actin gene were Forward 5'-ACGGTCAGGTCATCACTATCG-3`, and Reverse 5'-GGCATAGAGGTCTTTACGGATG-3'.[26]

Statistical Analysis

All data were presented as the mean ± standard deviation (SD). Paired t-tests were used to evaluate the levels of serum *IL-10* before and after intervention of high fiber diet. One way ANOVA was used to analyze the differences in *IL-10* serum levels and the expression of *IL-10* genes between the groups. Tukey's honest significant difference (HSD) was post hoc tests. Differences were considered statistically significant at $p<0.05$.

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Table 1: Analysis of serum IL-10 levels using ELISA method before and after high fiber diets

Group	n	Cytokine level of serum IL-10 (pg/mL)		Δ Mean (pg/mL)	Δ Mean (%)	p#
		Pre test	Post test			
Normal (N)	4	100.72±9.74	81.87±7.16	-18.85	17.87	0.042#
Hyperlipidemia (HL)	4	77.81±9.43[a]	104.21±10.29[a]	26.40	33.92	0.016#
Hyperlipidemia + diet containing 6.88 % fiber (HL1)	4	65.47±9.49[a]	123.83±2.75[b]	58.36	89.14	0.001#
Hyperlipidemia + diet containing 13.77 % fiber (HL2)	4	74.79±6.97[a]	130.65±4.72[b]	55.86	74.68	0.001#
Hyperlipidemia + diet containing 20.65% fiber (HL3)	4	76.80±9.95[a]	153.50±12.16[c]	76.70	99.86	0.002#
p*		0.251	0.001*			

Note : Data is displayed as mean±standard deviation (SD); * $p<0.05$ is considered as significant value; # $p<0.05$ is categorized as significant value; There were no significant differences in pre-test between groups $p>0.05$. Superscript [a,b,] and [c] indicate $p<0.05$ vs hyperlipidemia group according to One Way ANOVA test followed by Tukey HSD. P in row indicate the differences of serum IL-10 before and after high fiber diet in the same group. P in last row indicates the differences of plasma/serum IL-10 between group. [b, c] stated $p<0.05$ vs Hyperlipidemia group.

Results

The levels of serum *IL-10* before and after intervention of high fiber diet to hyperlipidemic rats are shown in Table 1. Before intervention, the levels of *IL-10* in the N group were higher than the HL or HL with high-fiber diet groups. It showed that high trans-fat

and fructose diet decrease *IL-10* levels, which may induce inflammation. However, after administration of the high-fiber diet, the serum levels of *IL-10* in hyperlipidemic rats increased significantly (p<0.05). In the present study, there was a decreased serum *IL-10* levels in normal control.

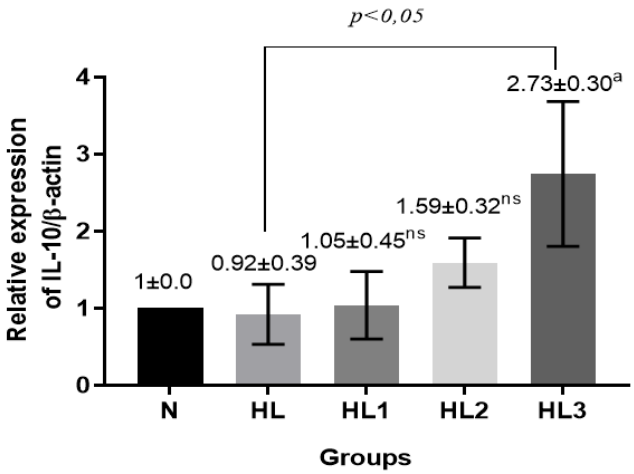

Fig.1: Expression of IL-10 on white adipose tissues of rats after administration of high fiber diet comparing those received normal diet. N: Normal control group; HL: Hyperlipidemia group; HL1: Hyperlipidemia + diet containing 6.88 % fiber; HL2: Hyperlipidemia + diet containing 13.77 % fiber; HL3: Hyperlipidemia + diet containing 20.65% fiber. Superscript a and b indicate p<0.05 vs hyperlipidemia group according to One Way ANOVA test followed by Tukey HSD

This study showed that the diet with 20.65% fiber could significantly increase *IL-10* gene expression in HL3 (p<0.05). The diet containing 13.77% fiber can also increase *IL-10* gene expression in HL-2, although it was not statistically significant. It showed that high fiber diet could decrease inflammation through increase the gene expression and levels of *IL-10*. (Figure 1).

Discussion

In the current study, the rats consumed a high-fat and fructose diet for 7 weeks, in the pre-test, had lower serum *IL-10* levels compared to a normal diet (Table 1). This showed that the diets high in fat and fructose could induce a decrease in *IL-10* anti-inflammatory cytokines. High fat diet is reported to induce systemic chronic low-grade inflammation.[27]

High fat diet increases free fatty acid levels that may directly act on intestinal cells, and lead to elevated production of pro-inflammatory[27] or decrease anti-inflammatory cytokines. High plasma FFAs could upregulate the expression of TLRs in circulating macrophages, enabling macrophages to be activated (M1 phenotype).[27] M1 macrophages secrete TNF-α, IL-1 and MCP-1 to recruit monocytes to adipose tissue and increase the ratio of M1: M2 macrophages that cause a decrease in *IL-10* cytokines. The decrease in M2 macrophages can reduce *IL-10* levels because M2 macrophages in adipose tissue are important in secreting anti-inflammatory cytokines, especially *IL-10*, and are involved in maintaining homeostasis in white adipose tissue.[28] Therefore, high fat diet causes an increase in proinflammatory cytokines and a decrease in *IL-10* levels (Kondo *et al.,* 2018).[29]

On the other hand, FFA molecules can act as signal transducer molecules that can bind to TLR 2 and TLR 4. Activation of TLR2 and TLR4 will trigger activation of NFkB which causes the release of proinflammatory cytokines and decreased *IL-10* levels.[7,6]

According to Zhu *et al.,*[30] FFA can increase regulation of TLR2 and TLR 4 gene expression when triglycerides (TG), total cholesterol (TC) or both increased.

In this study, both *IL-10* gene expression and *IL-10* levels in hyperlipidemia rats group were higher than those in normal control rats group. This may be an effect of adipose tissue compensatory mechanism. According to Juge-Aubry *et al.,*[31] the adipose tissues always produces anti-inflammatory factors to limit pro-inflammatory effects. *IL-10* is one anti-inflammatory factor that will be enhanced to limit TNF-α response during compensation. During acute inflammation, release of pro-inflammatory molecules such as IL-1 and TNF-α is followed by release of local anti-inflammatory mediators such as *IL-10* to act as offset agents.[32] Stoecklin *et al.,*[33] stated that increased expression of *IL-10* mRNA was thought to be due to an increase in TNF-α mRNA 3-5 h after such an increase. The TNF-α may activate *IL-10* gene expression in monocytes. [33]

Administration of high fiber diet for 6 weeks was able to increase significantly ($p<0.05$) *IL-10* levels in hyperlipidemia rats (HLT1, HLT2, HLT3). Fiber could not be digested by the small intestine enzymes but it would be fermented by colonic bacteria to produce short-chain fatty acids (SCFAs), especially butyrate, propionate and acetate. Butyric and propionate acids were reported to have anti-inflammatory activity.[34,35] Sasaki *et al.,*[36] reported that adequate amounts of fiber would increase the fermentation yield of SCFA, for instance, butyric acid. The study by Nastasi *et al.,*[37] showed that butyrate could suppress TNF-α, IL-6 via monocytes and macrophages and may increase the release of *IL-10* anti-inflammatory cytokines.

In hyperlipidemia rats, the increase of *IL-10* levels after giving of high fiber diet may relate to elevate *IL-10* gene expression. SCFAs have a possibility to modulate the expression of the *IL-10* gene at the mRNA transcription stage. This mechanism accordances with research by Astakhova *et al.,*[38] found that SCFA could limit the activity of HDAC in the nucleus. The inhibition of HDAC activity will give access for transcription factors to the promoter and will provoke gene expression. Besides the effect of high fiber diet intervention, increased *IL-10* serum levels in the intervention groups may also be supported by compensatory mechanisms after induction of high trans-fat and fructose. However, the increased *IL-10* serum levels in the intervention groups between 2x until 3x compared to the hyperlipidemia rat group without intervention. Therefore, it showed that high-fiber diet could increase *IL-10* serum levels.

This study suggested that a high-fiber diet may act as an anti-inflammatory agent, by increasing level and *IL-10* gene expression in adipose tissue triggered by high-fat and fructose diets. Based on this study, high-fiber diet has a possibility to be an alternative therapeutic strategies in cases of hyperlipidemia and other cases involving inflammatory mechanisms such as obesity, diabetes mellitus and lipid-related cardiovascular disease. The limitation of this study is mainly that we did not perform the analysis of dietary fiber type.

Conclusion

High fiber diet could alleviate inflammation through increasing the gene expression and levels of *IL-10* in white adipose tissue of hyperlipidemia rats model.

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Conflict of Interest

The authors declare there is no conflict of interest to disclose.

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