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The Regulating Effect and Mechanism of LJPS on Serum Lipids in ApoE-/- Mice of Atherosclerostic Hyperlipidemia

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Abstract **Aim:** To study the regulating effect and possible mechanism of Laminaria japonica polysaccharide (LJPS) on serum lipid in ApoE-/- mice of atherosclerostic hyperlipidemia. **Methods:** Twenty healthy male ApoE-/- mice were established atherosclerostic hyperlipidemia models by feeding with fat-rich diet for 12 weeks and and were randomly divided into model group and treated groups, ten healthy male C57BL/6J mice fed with ordinary feed as the control group. The mice in the treated group were gavaged LJPS once every other day for 4 weeks, while the mice in the control and model groups were simultaneously given equal volume saline. The serum levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol C (LDL-C) and high-density lipoprotein cholesterol C (HDL-C) were detected by biochemical assay. The activity of lipoprotein lipase (LPL) and hepatic lipase (HL) were determined by chemical colormetry. Enzyme-linked immunosorbent assay (ELISA) was applied to determine the level of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and activity of HMG-CoA reducase (HMG-CR). The concentrations of malondialdehyde (MDA) and nitric oxide (NO) were respectively measured by thiobarbituric acid assay and nitrate reductase assay. The activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) were respectively determined by xanthinoxidase assay and chemical colormetry. **Results:** After treated with LJPS, the body weights of mice in the treated group were significantly decreased than that in the model group ($P<0.05$), and the serum levels of TG, TC and LDL-C were significantly decreased ($P<0.05$) while the HDL-C was significantly increased ($P<0.05$) than those in the model group. In treated group mice, the activities of LPL and HL in serum and hepatic tissue were significantly higher than those in model group ($P<0.05$), while the HMG-CoA level of hepatic tissue was significantly higher and the HMG-CR activity lower than those in model group mice ($P<0.05$). In the model group mice, the levels of MDA and NO in serum and hepatic tissue were lower, while the activities of SOD and GSH-PX were significantly higher than those in the model group mice ($P<0.05$). **Conclusion:** It is suggested that LJPS could regulate the lipid metabolism by enhancing the activities of LPL and HL and inhibiting the activity of HMG-CR, and by increasing the activities of SOD and GSH-PX to reduce the levels of MDA and NO.

Keywords: *LJPS, lipids, atherosclerosis, LPL, HL, HMG-CR, MDA, NO, SOD, GSH-PX, ApoE-/- mice*

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1. Introduction

Atherosclerosis is a kind of diseases characterized by the formation of fibrous plaques in the intima of blood vessels. It is a common chronic inflammatory disease and the main pathological basis of vascular diseases [1,2]. Hyperlipidemia is a common and frequently-occurring syndrome in metabolic diseases and closely related to vascular diseases [3]. Reducing serum levels of lipids is a effective measure of preventing and treating vascular diseases. Currently, the fibrates [4] and statins [5] were clinically used to regulate lipid metabolism to reduce serum levels of triglyceride (TG) and total cholesterol (TC). Lipoprotein lipase (LPL) is a key enzyme in the process of lipid metabolism, which can lead the TG and very low-density lipoprotein (VLDL) to advance, and then cause the metabolic disorder of other lipoprotein [6]. Hepatic lipase (HL) is also a enzyme in the process of lipid metabolism, which effect on the decimpose of lipoprotein microparticle and affect the conversion process of LDL and high-density lipoprotein (HDL), when the synthesis or activity abnormality all can cause the metabolic disorder [7]. Hydroxy-methyl-glutaryl coenzyme A (HMG-COA) reductases (HMG-CR) which

is the rate-limiting enzyme in the process of cholesterol synthesis, is the target enzyme in treating atherosclerosis, coronary artery disease and cerebrovascular diseases, so inhibiting the activity of the enzyme can reduce the synthesis of endogenic cholesterol [8]. The superoxide dismutase (SOD) is a enzyme to clear the free radicals and can guard the cell against damaging by getting rid of superoxide anion radical and reducing the lipid peroxides production [9]. Glutathione peroxidase (GSH-PX) is a kind of significant catalyze enzyme which is extensively existed inside of the body. Malondialdehyde (MDA) is the last metabolite of lipid peroxidation which produced in the metabolization of oxygen radical in organism, which can reflex the content of oxygen radicals' metabolites by the MDA gallery level. Kelp belongs to Laminaria japonica which composed mainly kelp polysaccharide, Laminine, and many trace elements [10]. Many physiologic functions of kelp closely related to the biological activity of Laminaria japonica polysaccharide (LJPS) could increase the immunological activity of organism and exhibited anti-aging effects [11], nonetheless, few research on the reducing blood lipids and antioxidation were reported [12]. This study aim to explore the regulating effects of LJPS on blood lipids and its possible mechanismon atherosclerostic hyperlipidemia ApoE-/- mice.

2. Materials and Methods

2.1. Laboratory Animals

2.1.1. Animal Source

Ten C57BL/6J mice and twenty ApoE-/- mice, male, 6 weeks old, SPF grade, body mass (20 ± 2) g, purchased from Hangzhou Ziyuan Experimental Animal Science and Technology Co. Ltd.: SCXK (Zhejiang) 2019-0004. All animals were acclimatized for 7 days and allowed free access to food and water in a temperature at (23 ± 2) oC and humidity-controlled 12h/12h day and night environment. The local legislation for ethics of experiment on animals and guidelines for the care and use of laboratory animals were followed in all animal procedures. The experimental steps strictly comply with the ethical requirements of animal welfare.

2.1.2. Establishment of Model

ApoE-/- atherosclerosis mouse model was established by fat-rich diet [13]. Fat-rich feed (D12108C) was purchased from Jinan Pengyue Experimental Animal Breeding Co. Ltd. Which composed of corn starch 23.51%, casein 22.18%, cocoa butter 17.19%, sucrose 12.53%, maltodextrin 7.87%, cellulose 5.54%, soybean oil 2.77%, potassium citrate 1.83%, calcium phosphate 1.44%, cholesterol 1.25%, mineral premix 1.11%, vitamin premix 1.11%, calcium carbonate 0.61%, sodium cholate 0.50%, cystine 0.33%, choline 0.22%. The model was successfully established after 12 weeks of continuous feeding by fat-rich diet [14,15].

2.2. Grouping and Intervention

2.2.1. Laminaria Japonica Polysaccharide (LJPS)

The good variety Laminaria japonica powder "Zhongke No.1" were used as material feeder which was originally selected and harvested from Rongcheng, Shandong. The main components are dietary fiber 26.1%, protein 8.5%, lipid 0.39%, the total amino acid 10.49 mg/100g, vitamin A 273 μg/100g, vitamin C 3 μg/100g. The Laminaria japonica was cut into granular powder, the general forage 90% and the Laminaria japonica powder 10% were blend and fine-extracted into LJPS.

2.2.2. Grouping and Intervention

Ten C57BL/6J mice were randomly assigned to the control group. Twenty ApoE-/- mice successful modeled were randomly divided into model group and treated group consisting of 10 mice respectively. The mice of treated group were gavaged LJPS which dissolve with normal saline into 1 mL (equivalent to 2 g/kg body weight) once every other day for 4 weeks. The mice in the control group and the model group were given equal volume of normal saline for 4 weeks.

2.3. Sample Collection

2.3.1. Serum

At the end of this experiment, all mice were forbid food for 12 h, and then and 10% chloral hydrate solution was intraperitoneally injected (300 mg/kg) for anesthesia. Then 1 mL of blood was taken from the heart and separated by a low speed centrifuge at 4000 rpm for 10 min and stored in a -20°C.

2.3.2. Hepatic Tissue

After taken blood from the heart, the hepatic tissue 0.2 g was immediately collected and the rudimental blood with normal saline and grind fully on -4°C ice bath. The hepatic tissue sample was centrifugalize for 10 min at 12000 rpm to separate the supernatant and stored at -20°C.

2.4. Examination Indexes

2.4.1. General Condition

The body mass of mice was measured once two weeks, and the mental state, fur gloss, activity and body mass of mice in each group were observed.

2.4.2. Blood Lipid Detection

The serum levels of TG, TC, LDL-C, and HDL-C were detected by the Automatic Biochemical Analysis System (Modularp 800, Roche, Switzerland). The sensitivity is mmol/L.

2.4.3. Chemical Colormetry

The activities of LPL and HL were detected by chemical colorimetry with the kits (Jiancheng Institute of Biomed. Tech., Nanjing China). Usually 100 μL of serum or hepatic tissue supernatant were used for determining the free fat acid and calculating the activities of LPL and HL. Standardization were conducted before the detection, and the ultraviolet spectrophotometer (Bechmann DU640, USA) was selected wavelength at 550 nm for determination. The sensitivity is U/mL.

2.4.4. Enzyme-linked IMMUNOSORBENT Assay (ELISA)

ELISA was used to determine the level of HMG-CoA and activity of HMG-CR. Usually 100 μL of serum or hepatic tissue supernatant were used to determine HMG-CoA and HMG-CR with the kits (QnSsytemsTM Co. Ltd.). Standardization were conducted before the detection, the selected wavelength was 450 nm for the Enzymeter (Bio-Rad 550, USA). The sensitivity of HMG-CoA and HMG-CR are μg/L and U/mL respectively.

2.4.5. MDA and NO

The values of MDA and NO were detected respectively by thiobarbituric acid and nitratase reduase method with the kits (Jiancheng Institute of Biomedical Technology, Nanjing China). Standardization were conducted on the ultraviolet spectrophotometer (Bechmann DU640, USA) and the selected wavelength were 532 nm (MDA) and 550 nm (NO) respectively. The sensitivity is nmol/L(MDA) and μmol/L (NO) respectively.

2.4.6. SOD and GSH-PX

The values of MDA and NO were detected respectively by xanthinoxidase assay and chemical colorimetry with the kits (same as MDA and NO). Standardization were conducted on the ultraviolet spectrophotometer and the selected wavelength were 550 nm (SOD) and 412 nm (GSH-PX) respectively. The sensitivity is U/mL.

2.5. Statistical Analysis

SPSS26.0 statistical software was used for analysis. Image J was used to read image information, and GraphPad Prism 6.0 software was used for drawing. Mean ± standard deviation of data between groups (± s) means that the difference between groups is significant (P<0.05).

3. Results

3.1. The Effect of LJPS on Body Mass of Mice

During the experiment, the control group mice had good mental status, bright fur, flexible activities, and no significant changes in body mass (P>0.05). Before modeling, the mice had good mental state, bright fur and flexible activities. After modelling, the mental state of the mice was slightly worse, the body was relatively obese, and the body mass was significantly higher than before modelling (P<0.05). After treatment, the body mass of mice in the treated group decreased than that in the model group (P<0.05). See Table 1.

Table 1. Effect of LJPS on body mass of mice ($\bar{x}$± s, n=10)

Groups	Before modelling (g)	After modelling (g)	After treatment (g)
Control group	19.38±1.13	29.97±0.79	29.95±0.93
Model group	20.14±0.81	30.84±1.89	31.53±1.10
Treated group	20.04±0.74	31.30±1.21	30.25±1.03#

# P<0.05 vs model group

3.2. The Effect of LJPS on Serum Levels of Lipid in Mice

At the end of the experiment, the serum levels of TC, TG and LDL-C in the model group mice were significantly increased (P<0.01), while HDL-C were significantly decreased (P<0.05) than those in the control group mince. And the serum levels of TC, TG, LDL-C in the treated group mice were significantly lower (P<0.05), while the level of HDL-C was significantly higher than those in the model group mice (P<0.05). See Table 2.

Table 2. Effect of LJPS on serum levels of lipids in mice ($\bar{x}$± s, n=10)

Groups	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Control group	0.36±0.11	2.39±0.27	1.32±0.20	0.15±0.05
Model group	1.30±0.67*	19.07±2.12*	1.04±0.17*	2.15±0.29*
Treated group	0.71±0.33#	13.33±3.38#	1.18±0.22#	1.52±0.51#

*P<0.01 vs control group, #P<0.05 vs model group

3.3. The Effect of LJPS on the Activities of LPL and HL in Mice

The activities of LPL and HL in serum of the model group mice were significantly lower than those of the control group mice (P<0.05), while the treated group mice were significantly higher than those of the model group mice (P<0.05). The variations of LPL and HL activities in hepatic tissue are similar to that in the serum. See Table 3.

Table 3. The activities of LPL and HL after treatment ($\bar{x}$± s, n=10)

Groups	Serum LPL (U/mL)	Hepatic LPL (U/mL)	Serum HL (U/mL)	Hepatic HL (U/mL)
Control group	0.53±0.06	1.56±0.15	0.46±0.05	1.42±0.16
Model group	0.39±0.05*	1.10±0.14*	0.37±0.04*	1.12±0.16*
Treated group	0.70±0.08#	2.04±0.18#	0.59±0.08#	1.76±0.25#

*P<0.05 vs control group; # P<0.05 vs model group

3.4. The Effect of LJPS on the Value of HMG-CoA and Activity of HMG-CR

The value of HMG-CoA and activity of HNG-CR were too lower to be detected by ELISA. The value of HMG-CoA of hepatic tissue in model group mice was significantly lower, while the activity of HMG-CR was higher than that in control group mice (P<0.05). The activity of HMG-CR of hepatic tissue in treated group mice was significantly lower than that in model group mice (P<0.05). See Table 4.

Table 4. The value of HMG-CoA and the activity of HMG-CR after treatment ($\bar{x}$± s, n=10)

Groups	Hepatic HMG-CoA (μg/L)	Hepatic HMG-CR (U/mL)
Control group	26.86±2.79	21.23±3.12
Model group	20.13 ±2.91	35.43±3.75*
Treated group	27.92 ±2.37#	25.22±3.16#

* P<0.05 vs control group; # P<0.05 vs model group

3.5. The Effect of LJPS on the Values of MDA and NO

The results showed that the values of MDA and NO in serum of model group mice were significantly higher than those of control group mice (P<0.05). The values of MDA and NO in serum of treated group mice were significantly lower than those of model group mice (P<0.05). The variations of MDA and NO activities in hepatic tissue are similar to that in the serum. See Table 5.

Table 5. The valves of MDA and NO after treatment ($\bar{x}\pm s$, n=10)

Groups	Serum MDA (nmol/L)	Hepatic MDA (nmol/L)	Serum NO (μmol/L)	Hepatic NO (μmol/L)
Control group	6.71±0.82	5.56±0.36	20.93±2.89	21.43±3.67
Model group	9.67±0.87*	6.78±0.76*	26.11±2.32*	26.15±3.71*
Treated group	6.16±0.82#	5.70±0.34#	21.27±2.46#	21.46±3.26#

* P<0.05 vs control group; # P<0.05 vs model group

3.6. The Effect of LJPS on the Activities of SOD and GSH-PX

The results indicated that the activities of SOD and GSH-PX in serum of model group mice were significantly lower than those of control group mice (P<0.05). The activities of SOD and GSH-PX in serum of treated group mice were significantly higher than those of model group mice (P<0.05). The variations of SOD and GSH-PX activities in hepatic tissue are similar to that in the serum. See Table 6.

Table 6. The activities of SOD and GSH-PX after treatment ($\bar{x}\pm s$, n=10)

Groups	Serum MDA (U/mL)	Hepatic MDA (U/mL)	Serum NO (U/mL)	Hepatic NO (U/mL)
Control group	240.93± 9.94	608.87± 48.30	290.53± 8.11	428.16± 27.16
Model group	218.26± 7.77*	501.28± 53.18*	254.31± 7.05*	345.07± 22.06*
Treated group	246.35± 7.71#	587.86± 40.03#	285.92± 9.31#	393.64± 34.03#

* P<0.05 vs control group; # P<0.05 vs model group

4. Discussion

4.1. The Regulating Effect of LJPS on Blood Lipids

Lipid metabolic disorders were generally considered as a crucial risk factor to the occurrence of hyperlipidemia [16]. It is therefore need to conduct the treatment of reducing TG, TC, LDL and increasing HDL to patients with lipid metabolic disorder patients, and control actively the other risk factors to reducing vascular diseases caused by hyperlipidemia [17]. In the lipid metabolism, lipoprotein lipase (LPL) and hepatic lipase (HL) were the key enzymes [18], and the LPL resolved TG in chylomicron (CM) and very low density lipoprotein (VLDL), and transferred the TC, phospholipid (PHL) among the lipoproteins. The metabolized VLDL could translate into intermediate-density lipoprotein (IDL). The HL located on the surface of the hepatic endothelial cell, and participated in the transition process of IDL and LDL. The analytical IDL could be in-taken by hepatocyte and resolved the PHL and TG of HDL-2 selectivity, then transfer HDL-2 into HDL-3, finally the activated HPL HL reduced values of TG, TC and LDL in blood [19].

The dynamic cholesterol balance in cells is mainly dependent on two kind of regulating mechanisms: extra-cellular LDL receptor absorbing external cholesterol and intra-cellular cholesterol synthesis which the later one was catalyzed by HMG-CR. The HMG-CR is the key enzyme of cholesterol analysis for organism. The molecular structure of statins drugs is similar to HMG-CR's natural substrate HMG-CoA, so that the statins drugs are the competitive inhibitor for HMG-CR. The statins drugs inhibited the HMG-CoA transferring into the methylglutaryl acid in hepatocytes, and reduced the intra-cellular cholesterol analysis, then up-regulated the expression of LDL receptor on the hepatocyte membrane and get rid of LDL and VLDL in plasma acceleratively to reduce the LDL level in blood [20]. Clinical trials indicated that statins drugs could significantly decrease the serum values of LDL and reduce about 30% for the occurrence and mortality of cardiovascular diseases, while cause remarkably side effect as muscle pain with a lot of dosage [21].

In this experiment, after treatment using LJPS, the serum levels of TG, TC and LDL declined remarkably while the HDL higher than those in the model group. The results indicated the LJPS could also reduce the TG, TC and LDL and increase HDL values. Enzymatic activity tests showed that the activity of LPL and HL of serum and hepatic tissue in treated group were obviously higher, while the HMG-CR much lower than those in model group. It is suggested that the LJPS may influence TG, TC, LDL and HDL metabolism, and adjust blood lipids by activating enzymatic regulation on lipoprotein in hepatic tissue and inhibiting the HMG-CR activity to reduce internal cholesterol analysis.

4.2. The Anti-oxidant Effect of LJPS

Previous study reported that LJPS had obviously effects on anti-coagulation, spasmolysis, hypotensive, hypolipemic, expanding vessels and improving microcirculation in vascular disease [12]. Animal experiment indicated that LJPS could directly get rid of peroxide ion free radicals and hydroxy free radicals in vitro and ex vitro, and could enhance antioxidant enzymes activities of serum and tissue in vitro [22].

Malondialdehyde (MDA) was the last substance during the lipid peroxidation, which could yield oxygen radical in organisms and accelerate oxygen radical generation [23]. Nitric oxide (NO) is a important signal and effective molecule of organism [24]. If NO was exceptional or the homeostasis in the system oxidize/ antioxidation, it would resulted in the consistency of oxygen radical abnormally high, aggravate oxygen radical pathologically and accelerate the cell senescence, finally produced a premium on disease. In this study, we found that the MDA and NO values in model group increased than those in control group, which indicated that hyperlipermia could generate lipid

peroxidation, while the values of MDA and NO in the treated group were obviously decreased. It is concluded that the LJPS exhibited effects of antioxidation to regulating lipoprotein metabolism caused by hyperlipidemia.

Superoxide dismutase (SOD), a natural antioxidant enzyme catching free radical, could get rid of free radicals and guard the cell against damaging [25]. Glutathione peroxidase (GSH-PX) is another catalyze enzyme which was extensively existed, and protect the structure and function of epicyte, then interdiction the chain reaction of lipid peroxidation [26]. In the present experiment, the activities of SOD and GSH-PX in the treated group were obviously raised up than those in the model group, which suggested that LJPS can enhance anti-oxide activities, and then reduce lipid peroxidation. GSH-PX could also reduced lipid peroxide injury to reduce MDA level, therefore, LJPS could lighten various injury mediated by active oxygen species.

In summary, LJPS could regulate lipid metabolism by enhancing the activities of LPL and HL and by increasing the activities of anti-oxidase to reduce the level of lipid peroxidation.

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Ethics Approval and Consent to Participate

All related experiments were approved by the Experimental Animal Welfare Ethics Committee of Qingdao University (No. 20220917C573620230517080).

Conflicts of Interest Statement

The authors declare that there are no conflict of interest.

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