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Effects of low-deuterium liquor on coagulation and fibrinolytic system in experimental hyperlipidemia rats

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[Key words] liquor; low-deuterium water; hyperlipidemia; coagulation; fibrinolysis

[Abstract] Objective To study the effects of low-deuterium water and liquor on blood lipids, coagulation and fibrinolysis in hyperlipidemic rats. Methods A normal control group was set up. The hyperlipidemia model was established by continuous oral administration of liquor [0.01 L/(kg d)] or/and free drinking of deuterium-depleted water. The following indices were measured: Rat plasma triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, prothrombin time, activated partial thromboplastin time, tissue plasmin The thoracic aorta and liver of each group of rats were observed after hematoxylin-eosin staining. Results Compared with the high-fat model group, high-density lipoprotein and tissue plasminogen activator levels in the low-deuterium water group were significantly increased (P <0.05), and active plasminogen activator inhibitor 1 were significantly decreased (P <0 .05); low-density lipoprotein and active plasminogen activator inhibitor 1 in rats in the low-dose liquor group The inhibitor of prothrombin-1 was significantly decreased (P < 0.05), and the prothrombin time and tissue plasminogen activator were significantly increased (P < 0.05). Total cholesterol, high-density lipoprotein, prothrombin time and tissue plasminogen activator were significantly increased (P < 0.05); Total cholesterol, high-density lipoprotein, low-density lipoprotein, prothrombin time and tissue plasminogen activator were significantly increased (P < 0.05), triglycerides esters and active plasminogen activator inhibitor 1 were significantly reduced (P <0.05); total cholesterol, triglycerides and tissue fibrinolytic activity in the low-dose low-deuterium liquor group were significantly reduced (P <0.05); The zymogen activator level was significantly increased (P < 0.05), while the activated partial thromboplastin time and active plasminogen activator inhibitor 1 were significantly decreased (P < 0.05). When deuterium-depleted water and liquor were applied to high-fat rats, they could improve the coagulation and fibrinolytic systems of high-fat rats, thus protecting the cardiovascular system. When low-deuterium liquor was used on hyperlipidemic rats, the effect was not significantly different from that of ordinary liquor.

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Effects of Deuterium-Depleted Water and Liquor on Lipid Metabolism in Rat Models of Hyperlipidemia

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[KEY WORDS] Liquor ; Deuterium d-epleted Water; Hyperlipidemia; Blood Coagulation ;

[ABSTRACT] Aim To investigate the effects of deuterium d-epleted water (DDW) and liquor on lipid metabolism , blood coagulation and fibrinolysis activity in experimental hyperlipidemic rats.

Methods Normal control and hyperlip-idemia model groups were designed. Experimental hyperlipidemia rats were administration of liquor [(0 .01 L / (kg d)] or deuterium d-epleted water for 90 d. The levels of plasma triglyceride (TG), total cholesterol (TC), high d-ensity lipo-protein (HDL), and low d-ensity lipoprotein (LDL)were determined, and prothrombin time (PT), activated partial throm-boplastin time (APTT), tissue plasminogen activator (t -PA)activity , and plasminogen activator inhibitor l-(PAI 1-) activi-ty were measured. The pathological examination of the aorta structure and liver tissue was performed.

Results Com-pared with model group , HDL and t-PA significantly increased (P <0.05) and PAI 1-significantly decreased (P <0 .05)in DDW group. LDL and PAI 1-significantly decreased (P <0.05) and PT and t-PA significantly increased (P <0 .05) in low d-ose liquor group. Further , TC, HDL , and PT and t -PA in high d-ose liquor group significantly increased (P <0.05). The TC, HDL , LDL , and PT and t -PA significantly increased (P <0.05) and TG and PAI 1- significantly de-creased (P <0.05) in high d-ose liquor with DDW group. The TC , TG , and t-PA significantly increased (P <0.05) and APTT and PAI 1-significantly decreased (P <0.05) in low d-ose liquor with DDW group.

Conclusions Blood clotting system and fibrinolysis system in the experimental hyperlipidemic rats were improved by DDW and liquor , respectively. The combined effects of liquor and DDW on these 2 systems in hyperlipidemic rats were similar to those of liquor.

Excessive drinking has long been closely associated with various cardiovascular diseases. Related However, some recent studies suggest that moderate, regular drinking

Beneficial to the body, such as coronary heart disease, arteriosclerosis, thrombosis and myocardial infarction Death has a protective effect [2 -5] Despite the large number of epidemiological Study shows moderate drinking can reduce the risk of cardiovascular disease [6 -9] However, the potential harm of drinking in moderation [10] Long-term drinking has an average Impact of life expectancy [11] , and the impact of drinking habits on cardiovascular disease The impact of development [12,13] There are still uncertainties in the conclusions. Further research is needed.

Chinese liquor has a close relationship with water. People have long believed that Focus on how to use good water to improve the quality of wine and reduce the impact of wine on the human body As we all know, water in nature generally consists of 2 It is composed of 1 hydrogen atom and 1 oxygen atom, but the hydrogen atom has a different mass. The 3 isotopes of hydrogen (H) have a mass of 1, and the 2nd isotope of Heavy hydrogen (D), also known as deuterium; the mass of 3 is super tritium (T), also known as Tritium. The deuterium content in natural water is about 150 ppm. Research has found that deuterium is harmful to the survival, development and reproduction of life. Deuterium-depleted water (DDW) reduces carcinogenicity Gene expression, inhibition of cancer cell growth, radiation resistance and immune protection [14 -16] This experiment intends to use The effects of low-deuterium water, white wine, and low-deuterium white wine on hyperlipidemia rats were observed. Effects of deuterium-depleted water on the coagulation and fibrinolytic systems of rats It provides theoretical basis and experimental basis for the application of Yellow powder, 12% lard, 0.2% pig bile salt, 7% casein, 13% milk powder, 0.085% NaCl, 0.425% yeast powder) and saline stomach,

drinking normal water; (C) low deuterium water group (HF + DDW group): high The mice were fed with fat feed, given normal saline by gavage, and drank deuterium-depleted water; (D) liquor High-dose group (high-fat diets and high-dose liquor, HF + HL group): Liquor and distilled water were diluted in a ratio of 1:1 and then intragastrically administered. The mice were fed with high-fat diet and drank ordinary (E) high-fat diets and low-dose liquor group After HF +LL group): Dilute liquor and distilled water at a ratio of 1:5.7 release, the patient was given a high-fat diet. Feeding, drinking ordinary water; (F) low-deuterium liquor high-dose group (HF +HL +DDW group): Liquor and deuterium-depleted water were diluted in a ratio of 1:1 and then administered orally. At the same time, they were fed with high-fat diet and drank low-deuterium water; (G) low-deuterium liquor Low-dose group (HF +LL +DDW group): liquor and deuterium-depleted water were added according to The mice were diluted in a ratio of 1:5.7 and then gavaged, and fed with high-fat diet. The rats in each group were gavaged with 0.01 L/kg of water every day. The drug was continued for 90 days.

1.3 Sample collection

After the last administration, the subjects were fasted for 12 h, anesthetized 10% Chloral Hydrate by intraperitoneal injection, and blood was collected from the orbital vein. The serum was separated and placed on ice at -20 °C. After blood sample collection, the animals were killed by cervical dislocation and quickly Cut off about 1 cm of the lower segment of the thoracic aorta and remove the liver tissue. Formaldehyde fixation, dehydration, paraffin embedding, and sectioning.

1.4 Blood lipid measurement

The automatic biochemical analyzer was used to measure triglyceride (triglycer-TG) goes , and total cholesterol (total cholesterol) in blood samples. , TC), high-density lipid Protein (high density lipoprotein, HDL), low density lipoprotein The content of low density lipoprotein (LDL) and prothrombin time The value of prothrombin time , PT), activated partial thromboplastin time (activated partial thromboplastin time, APTT) is measured.

1.5 Tissue plasminogen activator and activated plasminogen activator Bioinhibitor 1 activity assay Tissue plasminogen activator , ELISA (tissue plasminogen activator inhibitor -1 1) , t-PA), active plasminogen activator activity.

1.6 Histological observation

Paraffin sections of thoracic aorta and liver tissue were obtained and hematoxylin-eosin Hematoxylin-eosin staining, HE staining, mounting, optical The pathological changes of both were observed under a microscope.

1.7 Statistical analysis SPSS 11.5

statistical software was used for statistical analysis. All experimental data were expressed as $x \pm s$, and t-test was used for comparison between groups. $P < 0.05$ was considered to be statistically significant.

2 Results

2.1 Changes in body weight of rats in each group During the

experiment, the body weight of rats in each group showed an increasing trend. After 30 days of the experiment, the body weight of rats in the hyperlipidemia group was significantly higher than that in the normal control group ($P < 0.05$), and this growth trend continued in the middle and late stages of the experiment. At the end of the experiment, the body weight of rats in the low-deuterium water group, the high-dose liquor group, the low-dose liquor group, and the low-deuterium liquor high-dose group was significantly lower than that in the hyperlipidemia group ($P < 0.05$), and the body weight of rats in the low-deuterium

water group, the low-dose liquor group, and the low-dose liquor low-dose group was close to that of the normal control group, while the body weight of rats in the high-dose liquor group and the high-dose low-deuterium liquor group increased abnormally slowly (Table 1).

Table 1. Changes in body weight of rats in each group during the experiment (x ±s, g, n =10)

Table 1. The body weight of different group rats during ex-perish

Grouping	0 days	30 days	60 days	90 days
Normal control group	191 ±7	332 ±16 b	373 ±16 b	445 ±27 b
HF Group	193 ±5	350 ±15 a	407 ±26 a	509 ±33 a
HF +DDW group	190 ±7	344 ±23	387 ±29	462 ±44 b
HF + HL group	190 ±5	307 ±8 ab	353 ±13 a b	393 ±28 ab
HF +LL group	193 ±7	336 ±18	386 ±22	468 ±35 b
HF +HL +DDW pair	193 ±6	303 ±36 ab	322 ±49 a b	362 ±38 ab
HF +LL +DDW group	188 ±6	343 ±24	386 ±27	506 ±35 a

a, P <0.05, compared with the normal control group; b, P <0.05, compared with the HF group.

2.2 Changes in triglyceride, total cholesterol, high-density lipoprotein and low-density lipoprotein levels in rats of each experimental group Compared with the rats in

the normal control group, the plasma TG and LDL levels of rats in the hyperlipidemia group were significantly increased, while the HDL content was significantly decreased, and the differences were statistically significant (P <0.05), indicating that the hypertriglyceridemia rat model was successfully established in this experiment. Compared with the model group, the TC and HDL levels in the low-deuterium water group increased significantly (P <0.05), and the TG and LDL levels showed a downward trend; the TC and HDL levels in the high-dose liquor group increased significantly (P <0.05), and the TG and LDL levels did not change significantly; the LDL level in the low-dose liquor group decreased significantly (P <0.05), and the TC, TG and HDL levels did not change significantly; the TC, HDL and LDL levels in the high-dose low-deuterium liquor group increased significantly (P <0.05), and the TG level decreased significantly (P <0.05); the HDL and LDL levels in the plasma of rats in the low-dose low-deuterium liquor group did not change significantly, while the TC and TG levels increased significantly (P <0.05) (Table 2). 2.3 Changes in plasma coagulation and fibrinolysis in rats in each experimental group

Compared with the normal control group, the plasma PT of the rats in the hyperlipidemia model group was significantly shortened (P < 0.05), and the APTT also tended to shorten, but the difference was not significant. The activity of t-PA was significantly decreased (P < 0.05), and the activity of PAI-1 was significantly increased (P < 0.05), indicating that the activity of the coagulation system of the hyperlipidemia rats was increased and the activity of the fibrinolytic system was decreased compared with the normal rats. Compared with the model group, the activity of t-PA of the rats in the deuterium-deficient water group was significantly increased (P < 0.05), and the activity of PAI-1 was significantly decreased (P < 0.05). The PT of the rats in the high-dose liquor group was significantly prolonged (P < 0.05), and the activity of t-PA was significantly increased (P < 0.05). The plasma PT of the rats in the low-dose liquor group was significantly prolonged (P < 0.05), and the APTT tended to be prolonged but not significant. The activity of t-PA was significantly increased (P < 0.05), and the activity of PAI-1 was significantly increased (P < 0.05). The activity of PAI-1 was significantly decreased (P < 0.05); the PT of rats in the high-dose low-deuterium liquor group was significantly prolonged (P < 0.05), the t-PA activity was significantly increased (P < 0.05), and the PAI-1 activity was significantly decreased (P < 0.05); the APTT of rats in the low-dose low-deuterium liquor group was significantly shortened (P < 0.05),

the t-PA activity was significantly increased ($P < 0.05$), and the PAI-1 activity was significantly decreased ($P < 0.05$) (Table 3).

Table 2. Changes in plasma TG, TC, HDL, and LDL levels in rats of each experiment (x ±s, n =10)

Table 2 . The plasma TG, TC , HDL and LDL concentration of different group rats

Grouping	TG(mmol/ L)	TC (mmol/L)	HDL(mmol / L)	LDL(mmol /L)
Normal control group	0.64 ±0 .12 b	1.34 ±0 .19	0 .51 ±0.08 b	0.20 ±0.02 b
HF Group	0.95 ±0 .24 a	1.41 ±0 .13	0.43 ±0.06 a	0 .34 ±0.05 a
HF +DDW group	0.88 ±0 .21 a	1.61 ±0 .08 ab	0 .50 ±0.06 b	0.28 ±0 .05
HF + HL group	1.01 ±0 .23 a	2.25 ±0 .17 ab	0 .84 ±0.09 ab	0 .39 ±0.03 a
HF +LL group	1.09 ±0 .24 a	1.34 ±0 .18	0 .48 ±0.07	0.26 ±0.05 b
HF +HL +DDW group	0.68 ±0 .12 b	2.22 ±0 .12 ab	0 .83 ±0.06 ab	0.44 ±0 .04 ab
HF +LL +DDW group	1.68 ±0 .40 ab	1.63 ±0 .09 ab	0.42 ±0.04 a	0 .36 ±0.04 a

a, P <0.05, compared with the normal control group; b, P <0.05, compared with the HF group.

Table 3. Changes in plasma PT, APTT, t-PA and PAI-1 levels in rats in each experiment (x ±s, n =10)

Table 3 . The measurements of plasma PT, APTT, t-PA and PAI -1 of different group rats

Grouping	PT(s)	APTT(s)	t -PA(ÿg / L)	PAI-1 (ng/L)
Normal control group	19.07 ±1 .00 b	26.48 ±5.01	18.44 ±2.89 b	739.41 ±101 .68 b
HF Group	15 .80 ±0.51 a 16	21.52 ±1.32	8.06 ±4.67 a	856 .33 ±111 .24 a
HF +DDW group	.20 ±1.24 a	20.63 ±2.25	24.32 ±4 .3 b	643.67 ±192.63 a b
HF + HL group	18.02 ±1 .06 b	22.12 ±3.22	16.06 ±3.48 b	818.67 ±184.24
HF +LL group	17.40 ±1 .32 b	24.06 ±7.58	13 .90 ±3.25 ab	426.67 ±132.53 a b
HF +HL +DDW group	17.68 ±0 .94 b	21.24 ±3.64	22.77 ±3.84 b	632.00 ±73.03 ab
HF +LL +DDW group	16 .30 ±1.19 a	17.90 ±2.16 ab	15.91 ±3.28 b	414.22 ±76.67 ab

a, P <0.05, compared with the normal control group; b, P <0.05, compared with the HF group.

2.4 Hematoxylin-eosin staining of thoracic aorta and liver of rats in each experimental group

The thoracic aorta wall of rats in the normal control group was clear and thin intima. The middle smooth muscle layer is uniform without atrophy and has normal thickness, and the outer layer is loose and knotty. connective tissue (Figure 1A). Endothelial cells fall off, irregular bulges appear in the intima, and the smooth muscle of the media is prominent. The thoracic aorta wall of the low-deuterium water group was still clearly layered. The middle smooth muscle layer was not atrophied, was uniform, and had normal thickness (Figure 1C). The thoracic aorta intima of the rats in the other groups was smooth, without prominent atherosclerotic plaques. The three-layer structure of the inner membrane, the middle membrane, and the outer membrane is clear (Figure 1D , E , F , G). In the normal control group, the liver lobule structure was clear and the hepatocytes were neatly arranged. The hepatocytes were uniform in size, with centrally located nuclei and light red cytoplasm (Fig. 2A). The hepatocytes of the model group rats showed extensive ballooning degeneration. Irregular arrangement, nuclei are mostly squeezed to the edge of the cell, nucleoli are unclear, small

There were scattered punctate necrosis in the lobe (Figure 2B);

The structure was normal, the nucleus was centrally located, and the cytoplasm was abundant (Figure 2C); high doses of liquor Compared with the high-dose group of low-deuterium liquor, the hepatocytes showed ballooning degeneration, the nuclei were shrunken, and There are a lot of fat droplets, which is mainly characterized by alcoholic fatty liver pathology (Figure 2D, F). The cell cytoplasm was loose and cloud-like, and the nucleus was normal, which was better than that of the model group. There was a significant improvement (Figure 2E, G).

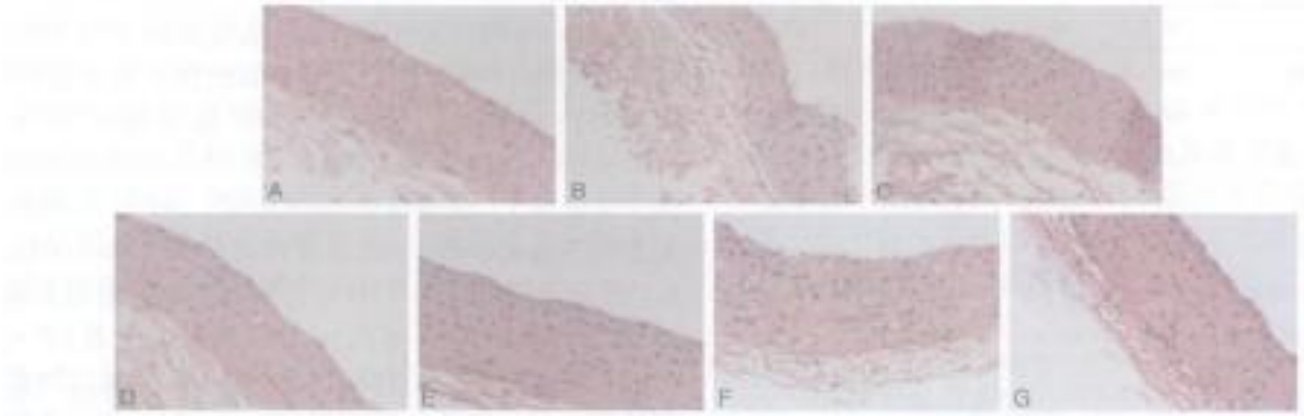

图 1. 各实验大鼠胸主动脉病理学观察(HE×40)

Figure 1. The pathologic observations of the aorta structure of different group

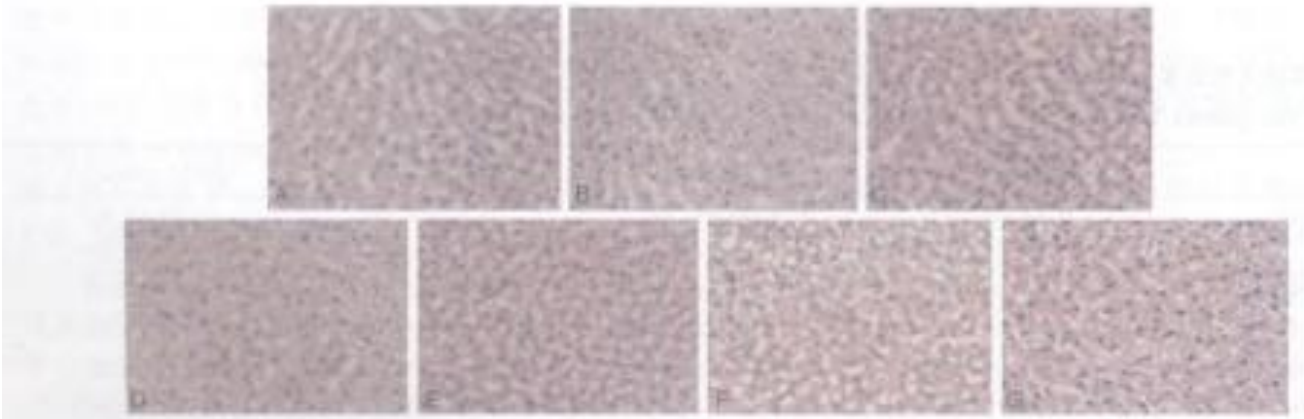

图 2. 各实验大鼠肝脏病理学观察(HE×40)

Figure 2. The pathologic observation of liver tissue of different group rats

3 Discussion

A large number of epidemiological studies have confirmed that moderate drinking has a negative impact on cardiovascular health. [17 ,18] , about the mechanism of alcohol protecting the heart The reason is still unclear, but there are reports [19 , 20] Points out that alcohol can make blood. Increased HDL in plasma plays a role in preventing coronary heart disease and atherosclerosis The oxidation products of LDL may be one of the main mechanisms of its protective effect. The most important factor mediating atherosclerosis. From the results of the body weight experiment, high doses of liquor and low deuterium The weight gain

of rats in the high-dose liquor group was abnormally slow, which we believe is Excessive alcohol intake leads to increased oxygen uptake during metabolism. The metabolic rate is increased, and ATP production during alcohol oxidation in the microsomes Drinking alcohol can increase triglycerides, but the difference is not significant. This may be because ethanol releases excessive amounts of Free fatty acids, drinking a lot of alcohol causes oxidative phosphorylation and fat in the body The ÿ-oxidation of fatty acids is impaired, which increases the free fatty acids in the blood and liver cells. In addition, fatty acids are synthesized into TG in the liver. The LDL content in the high-dose liquor group was significantly reduced, and the HDL It is true that drinking alcohol can increase plasma high-density lipoprotein The exact mechanism is still unclear, but some speculate that alcohol may promote liver Synthesis and secretion of apolipoprotein (APO) and increase [21] Triglyceride lipase activity, thereby increasing plasma HDL levels ÿ From the results of coagulation indexes, in the high-fat model group, the exogenous The PT of the activation degree of the coagulation pathway was significantly reduced compared with the normal control group. APTT, which reflects the degree of activation of the intrinsic coagulation pathway, also shortened. Short trend. This may be hypertriglyceridemia-VLDL ÿ (hypertriglyceridemia-very low density lipoprotein , HTG-VLDL) and chylomicrons (CM) make blood coagulation The activity of the factor increases, triggering the generation of a large amount of thrombin and causing the coagulation activity Enhanced, PT and APTT significantly shortened In addition, the high-fat model group The activity of PAI-1 in rats was significantly increased. The model group had slight thrombosis in the aorta intima, which was consistent with the relevant reports. Road [23] The plasma PAI-1 activity is consistent with that after thrombosis or vascular occlusion. The mechanism is that the activity of PAI-1 increases, which inhibits fibrinolysis. In this experiment, the t-PA activity in the high-fat model group was not significantly different from that in the control group. The difference may be due to the increase of PAI-1, which binds to t-PA. [24] Inactivation of t-PA ÿ The results of this study showed that both low-dose and high-dose Any amount of liquor can significantly prolong the PT of rats, indicating that liquor has It has anticoagulant function. Studies have shown that alcohol can cause the concentration of coagulation factors to increase. Decreased thromboxane synthesis, resulting in low coagulation system function Down [25] At the same time, rats in the low-dose liquor group and the high-dose liquor group PAI-1 activity was significantly reduced, and The activity of t-PA was significantly increased. the slices showed that the aortic intima morphology tended to be normal. Due to the anticoagulant function of alcohol and its ability to activate fibrinolysis, It protects against coronary heart disease, stroke and other cardiovascular diseases directly related to blood coagulation. Tumors provide the basis for [25], The results of this study showed that the blood lipids of rats with high blood lipids after drinking low-deuterium water The HDL content in plasma increased significantly, the activity of PAI-1 decreased significantly, and t-PA activity increased significantly, indicating that deuterium-depleted water can improve the blood However, low-deuterium liquor has an effect on high When the blood lipids of rats were tested, the effect was no different from that of ordinary liquor. Significant difference.

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