Preventive Strategies against Hyperlipidemia and Fatty Liver

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Abstract

We investigated the effects of hypocholesterolemic agents, fluvastatin, probucol and some traditional Chinese herbal medicines, i,e, Bofu-tsusho-san, Inchinko-to and Dai-saiko-to, on plasma levels of lipids and liver in male mice fed a high-fat diet. Plasma levels of lipids and the numbers of the fatty droplets in the liver cytoplasm were markedly lowered by the diets supplemented with these agents. Bofu-tsusho-san plus colestimide reduced plasma cholesterol levels in outpatients. Fish intake seems to lower plasma levels of lipids in Japanese postmenopausal women. Eicosapentaenoic acid or a high-fiber supplemented diets markedly lowered the plasma lipids and fatty droplets in the cytoplasm of liver cells in male mice fed a high-fat diet. The subjects with daily walking for more than one hour showed the lower plasma levels of total cholesterol. We investigated the effects of passive physical activity using a horse-riding machine on body features and plasma levels of lipids in volunteer. This exercise led the decreasing tendencies of body weight, BMI, systolic blood pressure, pulse rate, and plasma lipids. Thus, we propose some strategies for the treatment and/or prevention against hyperlipidemia and/or fatty liver, i.e. continuation of a physical exercise, intake of fish and fiber and, besides if necessary, taking of medicines such as statins, hypocholesterolemic drugs, marine-derived n-3 fatty acids and Kampo, traditional Japanese herbal medicines.

Key words —— hyperlipidemia, fatty liver, continuation of physical exercise, intake of fish and fiber, hypocholesterolemic medicines

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Recently, interest in multiple risk factor syndrome, a clustering of diabetes mellitus, hyperlipidemia and hypertension, has been increasing all over the world. The syndrome has been also called syndrome X[1)], deadly quartet visceral fat syndrome[2)] and metabolic syndrome[3)]. The Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) has proposed a definition for metabolic syndrome to aid in the identification of individuals at risk for both coronary heart disease (CHD) and type 2 diabetes[4)]. The definition incorporates thresholds for 5 easily measured variables linked to insulin resistance, i.e. waist circumference, triglycerides, high density lipoprotein (HDL) -cholesterol, fasting plasma glucose concentration and blood pressure, and this classification for metabolic syndrome is triggered when predefined limits of only 3 of the above 5 criteria are exceeded. On the other hand, the World Health Organization (WHO)'s definition of metabolic syndrome is more complex and is focused on glucose dysregulation[5)]. Thus, the NCEP's definition of metabolic syndrome rather than WHO's definition is expected to help identify individuals who may receive particular benefits from life style-related measures to prevent CHD and diabetes. Sattar *et al* [6)]. reported that,

according to the modified criteria of the NCEP, subjects with 4 or 5 of the features had a 3.7-fold increase in risk for CHD and a 24.5-fold increase in risk for diabetes compared with normal controls. Flegal *et al* [7]. indicated that the age-adjusted prevalence of obesity, i.e. a body mass index (BMI) of more than 30, was 30.5 % in 1999-2000 compared with 22.9 % in 1988-1994 in U.S.A.. The proportion of the population overweight, a BMI of more than 25, also increased during the same period, from 55.9 % to 64.5 %. Extreme obesity, a BMI of more than 40, also increased in the population, from 2.9 % to 4.7 %.

Fatty liver disease is a new clinicopathological entity of emerging importance, now recognized as the most common cause of abnormal liver. It is characterized by a wide spectrum of liver damage, i.e. simple steatosis may progress to advanced fibrosis and to cryptogenic cirrhosis via steatohepatitis, and ultimately to hepatocellular carcinoma[8]. It is suggested that chronic hepatocellular injury, necroinflammation, stellate cell activation, progressive fibrosis and ultimately, cirrhosis are initiated by the peroxidation of hepatic lipids and injury-related release of cytokines. Obesity is the single most significant risk factor for the development of fatty liver, both in children and in adults, i.e. obesity is also predictive of the presence of fibrosis, potentially progressing to advanced liver diseases. From a hystopathological point of view, insulin resistance plays a central role in the accumulation of triglycerides within the hepatocytes and in the initiation of the inflammatory cascade.

Accordingly, we have demonstrated the effects of hypolipidemic agents on the bases of our clinical and/or laboratory findings. Statins have been known to inhibit the production of mevalonate, a precursor for cholesterol and for geranyl-geranyl diphosphate, which is essential for prenylation of small proteins involved in signal transduction[9]. Statins increase the synthesis of cellular low density lipoprotein (LDL) receptors, causing a decrease in plasma levels of LDL[10] and have been known to slow the progression of CHD[11]. Fluvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, is a hypocholesterolemic agent effective in animals[12] and humans[13]. Accordingly, we investigated the effects of fluvastatin sodium on plasma levels of lipids and liver in male mice fed a high-fat diet[14]. Fluvastatin lowered the plasma levels of total cholesterol and the number of fatty droplets in the cytoplasm of liver cells, though the agent slightly affected the liver function. Probucol, 4,4' -isopropylidene-dithiobis (2,6-di-*t*-butylphenol), is also an effective hypocholesterolemic agent and is transported and incorporated into endothelial cell membranes to act as a radical-trapping antioxidant, protecting the endothelial cells against oxidative stress[15], and lowers an incidence of ischemic heart disease[16]. Thus, we investigated the effects of probucol on plasma levels of lipids and liver in male mice fed a high-fat diet[17]. Probucol markedly lowered the plasma levels of total cholesterol and triglyceride, and the number of fatty droplets in the cytoplasm of liver cells.

Furthermore, we required more harmless hypolipidemic agents. Some traditional Chinese herbal medicines have long been believed and used as anti-obese agents in China and Japan. Thus, we investigated the effects of Bofu-tsusho-san plus colestimide, which was an anion-exchange resin with an imidazolium salt on an epoxide polymer skeleton (2-methylimidazoleepichlorohydrin copolymer) , on body weight, plasma levels of lipids and fatty liver in 30 out patients[18]. Since an anion-exchange resin such as colestimide is not absorbed in the small intestine, decreases intestinal reabsorption of bile acids synthesized from cholesterol in the liver, and consequently increases bile acid excretion into the feces, no serious adverse effect of colestimide has yet been found. Chinese herbal medicines have generally been believed to cause few side effects at clinical doses. Their body weights tended to decrease slightly, and plasma levels of total cholesterol, but not triglyceride, were reduced after treatment. Fatty livers in only 2 cases were observed to recover well with the treatment. Inchinko-to contains three components, and has long been used as an anti-inflammatory, antipyretic, choleretic and diuretic agent for liver disorders and jaundice[19]. Bofu-tsusho-san contains 18 components, and has long been used against obesity[20]. Dai-saiko-to contains eight components, and has long been used as a hypocholesterolemic agent for liver disorders and as a therapeutic and/or preventive agent for cholesterol gallstone disease with hyper-triglyceridemia[21]. Accordingly, we investigated the effects of the three remedies on body growth, organ

weights, and plasma and liver lipids in young male mice fed a high-fat diet[22–24]. Plasma levels of lipids and the numbers of the fatty droplets in the liver cytoplasm were markedly lowered by the diets supplemented with three herbal medicines. The liver weights and the body growth were reduced by the diet supplemented with Dai-saiko-to, which slightly affected the concentrations of total protein, albumin, creatinine or calcium, and the activity of lactate dehydrogenase. Thus, the activities of anti-obesity, anti-hyperlipidemia and anti-hyperlipids in liver cells of Dai-saiko-to, besides Bofu-tsusho-san, seem effective in reducing body mass, liver lipids and lowering the plasma lipid level, when used carefully in an attempt to use for the prevention against metabolic syndrome-related diseases.

The American Heart Association has recommended consuming 2 fish meals (preferably oily fish) per week, which results in an intake of 400-500 mg docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA) /day, though improved data are required to determine dietary intake values or ratios among EPA, DHA, and EPA+DHA[25–27]. The Japan Public Health Center-Based Study, a 10-year prospective cohort study of 41,578 middle-aged Japanese, reported that dietary intake of marine-derived n-3 fatty acids has significant inverse associations with nonfatal coronary events[28]. Thus, we investigated the effects of fish intake on body features and plasma levels of lipids in postmenopausal women who underwent a medical check in the Yokohama district, Japan[29]. Fish intake tended to lower plasma triglyceride, total cholesterol and LDL-cholesterol levels, and slightly raise HDL-cholesterol levels. Accordingly, we investigated the effects of EPA on plasma levels of lipids and liver in male mice fed a high-fat diet[30]. EPA markedly lowered the plasma levels of total cholesterol and triglyceride, and the number of fatty droplets in the cytoplasm of liver cells, but the hemorrhagic events were not detected. Fatty diets composed of much meat and little fiber have been known to increase the risk of carcinogenesis, associated with hypercholesterolemia and hydroxyl radical formation[31]. Daily regular bowel movement, but not constipation or diarrhea, is necessary for healthy life. A high fiber weight reduction diet has been used to obtain regular bowel movement, frequently. However, it is also known to induce bone loss, which is not reversed by weight regain[32]. Thus, we investigated the effects of a high-fiber supplement on body growth, plasma levels of lipids and liver in male mice fed a high-fat diet[33]. A high-fiber supplemented diet markedly lowered the plasma levels of total cholesterol and triglyceride, and the number of fatty droplets in the cytoplasm of liver cells, but the tibial BMD was not affected.

It was reported that there were inverse correlations between physical activity and BMI and waist circumference, though there were positive correlations between age and BMI, waist circumference, triglyceride, total cholesterol and LDL-cholesterol[34]. Moderate to vigorous physical activity in nonbouts was reported to be a beneficial starting point for increasing physical activity levels and decreasing BMI and waist circumference[35]. Thus, we investigated the effects of physical activity on body features and plasma levels of lipids in postmenopausal women who underwent a medical check in the Yokohama district, Japan[36]. The subjects with daily walking for more than one hour showed the lower plasma levels of total cholesterol, but not triglyceride. On the other hand, the sedentary subjects also showed the lower plasma levels of total cholesterol. The reason was suspected to depend on the smaller appetites with lower physical activity. And then, we investigated the effects of passive physical activity using a horse-riding machine on body features and plasma levels of lipids in volunteer. Four physical activities of a 15-minute horse-riding per week for a month (total 240 minutes horse-riding) led the decreasing tendencies of body weight, BMI, systolic blood pressure, pulse rate, and plasma levels of total cholesterol and triglyceride[37].

In the present review, we proposed some strategies for the treatment and/or prevention against hyperlipidemia and/or fatty liver, i.e. continuation of a physical exercise, intake of fish (preferably oily fish) and fiber (including vegetables and dietary fiber) with a regular bowel movement as the prevention against the metabolic syndrome-related diseases and, besides if necessary, taking of medicines such as statins, hypocholesterolemic drugs, marine-derived n-3 fatty acids and Kampo, traditional Japanese herbal medicines as the treatments.

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高脂血症および脂肪肝に対する予防的戦略

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要旨

抗高脂血症剤であるフルバスタチン，プロブコールさらに漢方製剤である防風通聖散，茵蔯蒿湯，大柴胡湯が高脂肪飼料摂取マウスに与える影響について検討した結果，それぞれに血中脂質と肝細胞内脂肪小滴の減少が認められた．臨床では，防風通聖散の抗高脂血症効果が認められているが，本実験系では大柴胡湯に最も強い効果が認められた．閉経後婦人と魚介類摂取について検討した結果，魚介類とくに青魚を好んで食する婦人では血中脂質が低値であり，エイコサペンタエン酸（EPA）摂取マウスは高脂肪飼料摂取にも拘らず，血中脂質と肝細胞内脂肪小滴の減少が認められた．高繊維飼料摂取マウスでは高脂肪飼料摂取にも拘らず，血中脂質と肝細胞内脂肪小滴の減少が認められた．毎日 1 時間以上の歩行を日課としている閉経後婦人では血中コレステロールが低値を示していた．乗馬運動器具を用いての 1 ヶ月間の定期的な運動は，体重，BMI，収縮期血圧，脈拍数，血中脂質の低下傾向が認められた．以上の結果，高脂血症，脂肪肝の治療には，漢方製剤を含む抗高脂血症剤の服用を，そして予防的戦略として青魚を中心とした魚介類・高繊維食の摂取および身体運動活動の継続を提案する．

キーワード

高脂血症，脂肪肝，運動の継続，魚介類・緑黄色野菜・高繊維食の摂取，抗高脂血症剤の使用