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Abstract

The plasma fatty acid composition of cirrhotic patients and their dietary intake of fatty acids were determined. Significantly lower plasma arachidonic, docosahexaenoic, dihomo-gamma-linolenic and eicosapentaenoic acid levels were observed in cirrhotic patients than in healthy controls. A remarkably low dietary intake of polyunsaturated fatty acids supplied from fish, vegetable oil and pulses was shown in cirrhotic patients. Positive correlations were observed between plasma arachidonic acid concentrations and clearance rate of indocyanine green (KICG) (r = 0.826, p less than 0.05) and between dihomo-gamma-linolenic acid levels and cholinesterase activities (r = 0.841, p less than 0.05). From these results, we conclude that a supply of polyunsaturated fatty acids is necessary for the nutritional treatment of patients with liver cirrhosis.

KEYWORDS: lipid malnutrition, liver cirrhosis, polyunsaturated fatty acid

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Lipid Malnutrition of Patients with Liver Cirrhosis: Effect of Low Intake of Dietary Lipid on Plasma Fatty Acid Composition

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The plasma fatty acid composition of cirrhotic patients and their dietary intake of fatty acids were determined. Significantly lower plasma arachidonic, docosahexaenoic, dihomo-γ-linolenic and eicosapentaenoic acid levels were observed in cirrhotic patients than in healthy controls. A remarkably low dietary intake of polyunsaturated fatty acids supplied from fish, vegetable oil and pulses was shown in cirrhotic patients. Positive correlations were observed between plasma arachidonic acid concentrations and clearance rate of indocyanine green (K_{ICG}) ($r = 0.826$, $p < 0.05$) and between dihomo-γ-linolenic acid levels and cholinesterase activities ($r = 0.841$, $p < 0.05$). From these results, we conclude that a supply of polyunsaturated fatty acids is necessary for the nutritional treatment of patients with liver cirrhosis.

Key words: lipid malnutrition, liver cirrhosis, polyunsaturated fatty acid

A low-lipid and carbohydrate-enriched diet has been recommended for dietary treatment of patients with liver diseases, who have poor appetite and reduced absorption of lipid. Unsaturated fatty acids such as linoleic acid (C18 : 2 ω-6) and α-linolenic acid (C18 : 3 ω-3) are essential to higher animals, since they are not synthesized in the body and must be supplied from the diet. Therefore, long-term treatment of cirrhotic patients with a low-lipid diet may induce an essential fatty acid deficiency. Linoleic acid is converted to arachidonic acid (C20 : 4 ω-6) via dihomo-γ-linolenic acid (C20 : 3 ω-6) by chain elongation and desaturation in the liver. Dihomo-γ-linolenic, arachidonic, and eicosapentaenoic acids (C20 : 5 ω-3) are the precursors of prostaglandins which have potent biological activities. Gastrointestinal bleeding commonly observed in patients with liver cirrhosis might be caused by the deficiency of prostaglandin E_2 in gastric mucosa and juice (1). Thus, reevaluation of lipid nutrition is necessary for dietary treatment of cirrhotic patients.

In the present study, we determined the plasma fatty acid composition of cirrhotic patients and calculated their dietary fatty acid intake. Correlations between plasma fatty acid levels and dietary fatty acids and between the fatty acid levels and liver dys-

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function (clearance rate of indocyanine green (K_{ICG}) value and cholinesterase activity) were investigated.

Patients and Methods

Patients. Twenty-three cirrhotic patients (Table 1) admitted to Okayama University Hospital were studied. Patients with primary biliary and alcoholic cirrhosis were excluded from the study. None of the subjects had diabetes mellitus or hepatocellular carcinoma. Diagnoses of liver cirrhosis were made by histologic observations of the liver and by imaging procedures such as computed tomography and ultrasonography. Three patients had a history of hepatic encephalopathy, and eight of excess drinking. Ascites was observed in three, and jaundice in four patients.

Table 1 Clinical findings of 23 cirrhotic patients

Sex	Male	17
	Female	6
Age (years)		52±9[a]
Body weight (% of ideal body weight)		103±11
Skinfold (triceps+back) (mm)		25.8±13.2
Blood analysis		
Serum albumin (g/100 ml)		3.4±0.5
Fasted blood sugar (mg/100 ml)		109±35
Serum bilirubin (mg/100 ml)		1.37±0.71
Serum GPT[b] activity (IU/l)		58±48
Serum cholinesterase activity (IU/l)		199±82
Blood ammonia (μg/100 ml)		54±37
K_{ICG}[c]		0.07±0.03

a: Mean±SD.
b: Glutamic-pyruvic transaminase (alanine aminotransferase).
c: Clearance rate of indocyanine green.

Table 2 Food composition of the diet for liver cirrhotic patients

	(g/day)
Cooked rice	500
White bread	120
Fish (low lipid)	100
Meat	60
Egg	50
Milk	400
Soybean curd	200
Potato	70
Vegetable	300
Fruit	100
Sugar	20
Vegetable oil	10
Energy (kcal/day)	2,000
Protein (g/day)	90
Lipid (g/day)	50

Hospitalized control patients included seven patients (three males and four females, 32 years old on the average) suffering from rheumatoid arthritis, oroesophageal candidiasis, iron-deficiency anemia or chronic myelocytic leukemia (complete remission), but without liver disease. The healthy control group consisted of 12 males and 12 females in their twenties, 13 males and 3 females in their thirties, 6 males in their forties and a male in his fifties, who did not have liver dysfunction and who were not obese.

Methods. All of the cirrhotic patients had received a special diet usually served to the patient with liver disease in Okayama University Hospital (the liver diet) (Table 2) for at least 7 days prior to the present study. The hospitalized control patients had received a standard diet containing 2,200 kcal of energy, 80 g of protein and 60 g of lipid per day. Actual food consumption in these patients was calculated by weighing the served and residual food. The nutrient contents of the food and the fatty acid composition of the lipid were calculated according to food composition tables (2, 3).

Blood was obtained from a cubital vein following overnight (14 h) fast. Plasma fatty acid levels were routinely determined by gas chromatography with a Shimadzu gas chromatograph GC-8A (Shimadzu Seisakusho, Ltd., Kyoto, Japan)(4). Plasma phospholipids were separated by thin-layer chromatography (5) and the fatty acid composition was determined by gas chromatography. Plasma cholesterol, triglyceride, phospholipid and free fatty acid concentrations were determined by an automated routine clinical laboratory method.

Statistical analysis. Statistical analysis was done using Student's *t*-test and regression analysis. Data are expressed as the mean±SD, unless otherwise specified.

Results

Plasma lipids and fatty acid composition. Both plasma total cholesterol levels and the cholesterol ester ratio were lower than normal in 59% of the cirrhotic patients (Fig. 1). Plasma phospholipid levels were low in 38% of the patients. A significant correlation ($r = 0.947$, $p < 0.001$) was recognized between phospholipid and total cholesterol concentrations. Most of the cirrhotic patients showed a normal plasma triglyceride value. Elevation of plasma free fatty acid was shown in six patients (26%).

Table 3 Concentrations of polyunsaturated fatty acids in plasma total lipid

Fatty acid	Concentration (μg/ml)[a]	
	Cirrhotic patients	Healthy controls
Dihomo-γ-linolenic acid	15.1±3.5*	29.6±9.7
Arachidonic acid	63.4±15.4*	145.1±47.5
Eicosapentaenoic acid	21.5±10.1*	40.1±14.6
Docosahexaenoic acid	55.8±19.0*	94.3±20.3

a: Mean±SD. *, $p < 0.01$.

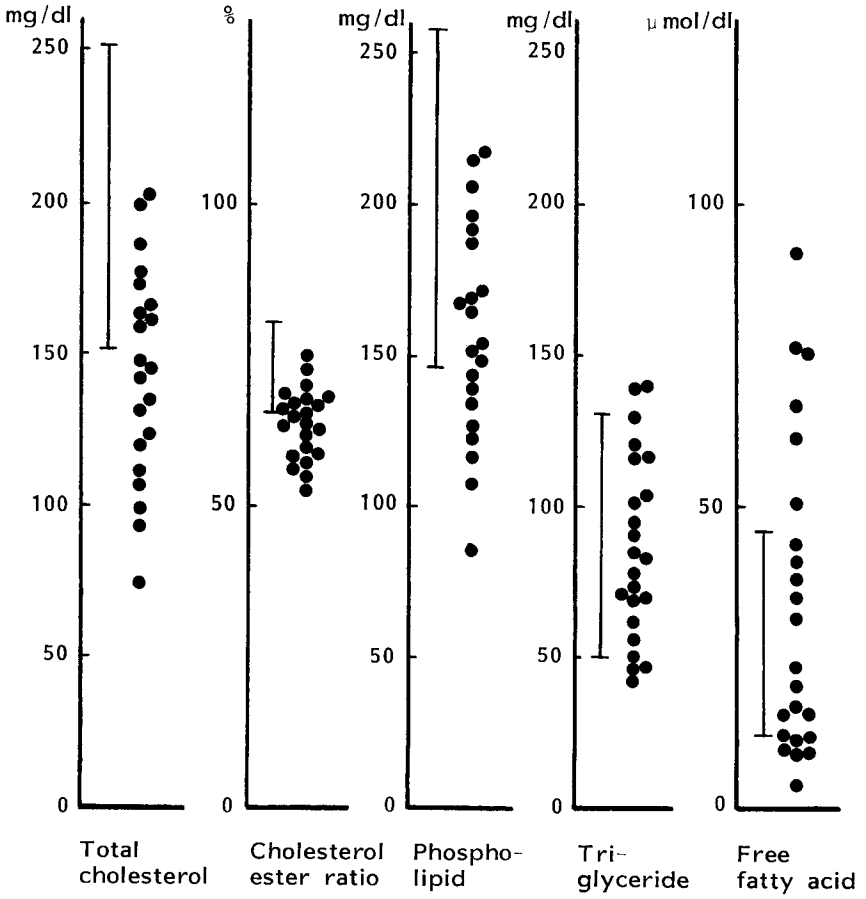

Fig. 1 Plasma lipid levels in cirrhotic patients. Vertical lines indicate the range of healthy controls.

Each plasma free fatty acid was represented as the percent of total plasma free fatty acids (Fig. 2). Oleic (C18 : 1), palmitic (C16 : 0) and linoleic acids accounted for 35.2±4.4%, 29.6±3.9% and 18.2±3.6%, respectively. The cirrhotic patients had low levels of arachidonic and stearic acids (C18 : 0). Linoleic acid also tended to be low. Other highly unsaturated fatty acids could not be detected in the plasma free fatty acid fraction.

The levels of polyunsaturated fatty acids in the plasma total lipid fraction in cirrhotic patients are shown in Table 3. Significantly lower plasma arachidonic, docosahexaenoic (C22 : 6 ω-3), dihomo-γ-linolenic and eicosapentaenoic acid levels were observed in cirrhotic patients than in healthy controls.

Dietary intake of nutrients and fatty acids. Table 4 shows the dietary intake of various nutrients by the cirrhotic and control patients. Lipid intake (36±17 g/day) and the lipid energy ratio (19±7%) were significantly lower in the cirrhotics than in control patients. There was no difference in lipid intake from meat, egg and milk (Table 5) between the cirrhotic and control patients. However, a significantly low level of lipid intake originating from fish, vegetable oil and pulses was recognized in cirrhotic patients. A remarkably lower dietary intake of polyunsaturated fatty acids (linoleic, α-linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acid) was shown by cirrhotic patients. The dietary polyunsaturated (P) : saturated (S) fatty acid ratio (P/S) was significantly ($p < 0.01$) lower in cirrhotic patients (0.80±0.08) than in control patients (1.66±0.12).

Relationship between dietary fatty acid composition, plasma fatty acid composition and liver dysfunction. The dietary P/S ratio correlated significantly to the plasma P/S ratio in cirrhotic patients ($r = 0.503$,

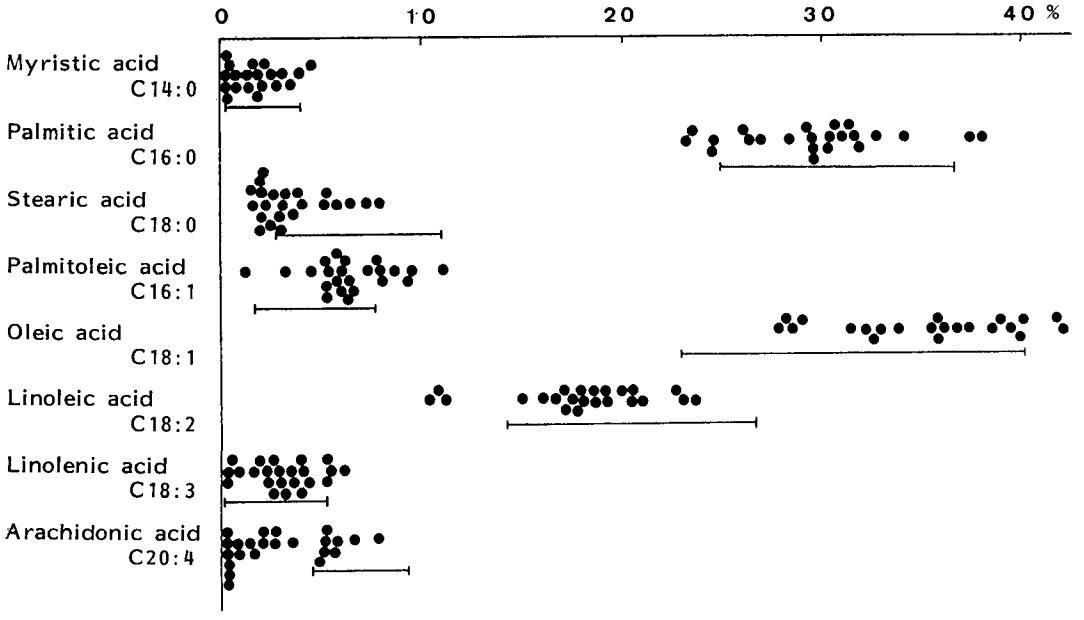

Fig. 2 Percent composition of plasma free fatty acids in cirrhotic patients. Horizontal lines indicate the range of healthy control subjects.

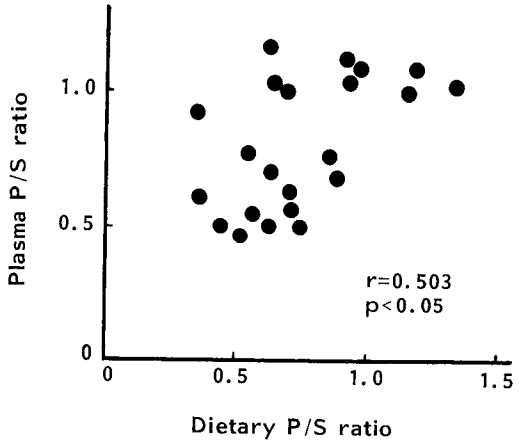

Fig. 3 Correlation between the dietary polyunsaturated fatty acid/saturated fatty acid (P/S) ratio and plasma P/S ratio in cirrhotic patients.

$p < 0.05$) (Fig. 3). The relation of liver function tests to the plasma polyunsaturated fatty acid concentration is illustrated in Fig. 4. A positive correlation was observed between the plasma arachidonic acid concentration and the K_{ICG} value ($r = 0.826$, $p < 0.05$). The plasma dihomo-γ-linolenic acid level correlated significantly with cholinesterase activity ($r = 0.841$, $p < 0.05$). However, the plasma eicosapentaenoic acid concentration did not show a significant correlation with the K_{ICG} value ($r = 0.684$, $p < 0.10$).

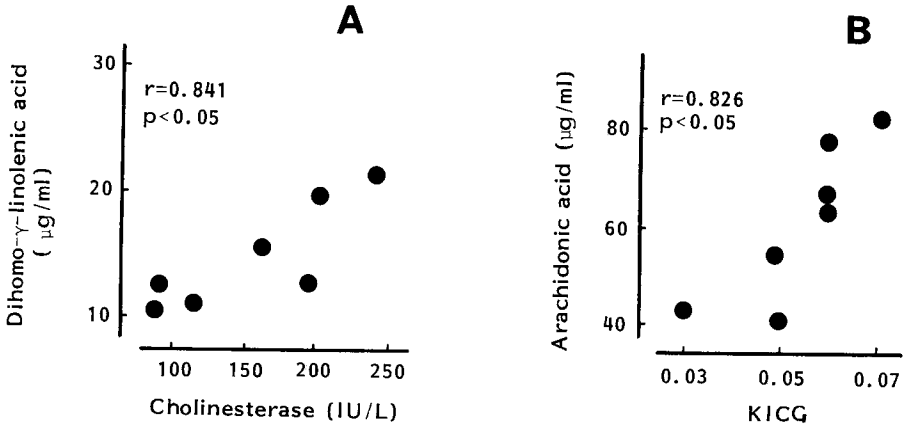

Fig. 4 Relationship between polyunsaturated fatty acid levels in the plasma and liver dysfunction (K_{ICG}, cholinesterase) in cirrhotic patients. A, Plasma choline esterase activity; B, clearance rate of indocyanine green (K_{ICG}).

Table 4 Dietary intake of nutrients

Nutrients	Intake/day[a]	
	Cirrhotic patients (Liver diet) n = 23	Hospitalized control patients (Standard diet) n = 7
Energy (kcal)	1,733±345	2,109±285
Protein (g)	70±24	76±3
Lipid (g)	36±17**	60±8
Carbohydrate (g)	274±63	272±68
Lipid energy ratio (%)	19±7*	26±3
Carbohydrate energy ratio (%)	64±12*	51±7

a: Mean±SD. **, $p<0.01$; *, $p<0.05$.

Table 5 Dietary intake of lipid and fatty acids

		Intake/day[a]	
		Cirrhotic patients (Liver diet) n = 23	Hospitalized control patients (Standard diet) n = 7
Total lipid (g)		36±3**	60±3
Meat, egg, milk		17±3	17±2
Fish		3±1*	8±1
Vegetable oil, pulses		13±1**	32±1
Fatty acids (g)			
Saturated fatty acids			
Myristic acid	C14 : 0	1.3±0.3	1.2±0.1
Palmitic acid	C16 : 0	7.0±1.3	9.4±0.4
Stearic acid	C18 : 0	2.0±0.4	3.2±0.4
Monounsaturated fatty acid			
Palmitoleic acid	C16 : 1	2.3±0.4	1.3±0.2
Oleic acid	C18 : 1	8.7±1.5**	15.3±0.9
Polyunsaturated fatty acid			
Linoleic acid	C18 : 2	6.2±1.8**	18.7±1.2
α-Linolenic acid	C18 : 3	0.6±0.1**	1.6±0.1
Arachidonic acid	C20 : 4	0.06±0.04**	0.22±0.05
Eicosapentaenoic acid	C20 : 5	0.11±0.05**	0.55±0.11
Docosahexaenoic acid	C22 : 6	0.27±0.09**	1.57±0.33
P/S ratio		0.80±0.08**	1.66±0.12
Cholesterol (mg)		380±41	438±81

a: Mean±SD. **, $p < 0.01$; *, $p < 0.05$.

Discussion

The results of the present study indicate that cirrhotic patients have an abnormal pattern of plasma free fatty acids. The low percent compositions of arachidonic and stearic acids and the high percent compositions of palmitoleic and oleic acids are consistent with previous reports (6). Plasma free fatty acid levels in cirrhotic patients have been shown to increase because of enhanced lipolysis (7). Free fatty acids are released from adipose tissue into the circulation, when there is need for fatty acid as a source of energy (8). Therefore, the plasma free fatty acid composition following overnight fast is similar to the composition in adipose tissue. The abnormal pattern of free fatty acids may be induced by changes in dietary habits and/or metabolic characteristics of adipose tissue (9).

As shown in Table 5, remarkably low intake of polyunsaturated fatty acids (linoleic, α-linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acid) was detected in the cirrhotic patients studied. Thus, dietary restriction of fatty fish and vegetable oil may lead to a low intake of dietary unsaturated fatty acid. The significant correlation between the plasma and dietary P/S ratios indicates that dietary therapy for cirrhotic patients might be useful. Modifying the dietary fatty acid composition with evening primrose oil (rich in linoleic acid and γ-linolenic acid) has been shown to alter clearly the composition of the plasma lipid

fraction (10).

Primary bile acids are produced in the liver and conjugate with glycine and taurine. These acids are extremely active in the formation of micelles. Lipid intake, therefore, has been restricted in liver diseases in which there is reduced biliary secretion. Chalmers *et al.* (11), however, reported that forced feeding with high-energy, high-protein and high-fat diet could well be tolerated and led to a rapid decrease in serum bilirubin in acute viral hepatitis. The recommended intake of lipid in Japan is 20-25% of total energy (12). The level of lipid intake of 48% of the cirrhotic patients in the present study did not reach the recommended level.

The low plasma concentration of dihomo-γ-linolenic acid and the close relationship between the concentration of this acid and serum cholinesterase activity might indicate that dihomo-γ-linolenic acid synthesis is depressed in the cirrhotic liver. Because dihomo-γ-linolenic acid is not found in food, the fatty acid distributed in the plasma must be synthesized from linoleic acid in the liver. The plasma arachidonic acid concentration correlated significantly with the K_{ICG} value. Arachidonic acid is also synthesized from linoleic acid via dihomo-γ-linolenic acid. Therefore, the significantly low concentrations of plasma dihomo-γ-linolenic and arachidonic acids in cirrhotic patients might be induced by their low-synthesizing ability. However, the possibility remains that the decrease in the synthesis of these fatty acid might originate in the decrease in the availability of the raw material, linoleic acid. Although in small quantity, arachidonic acid distributes widely in natural foods. Sufficient intake of polyunsaturated fatty acids from the diet appears to be important to the maintenance of a normal level of plasma lipids in cirrhotic patients.

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