Effects of Dietary α-Linolenic, Eicosapentaenoic and Docosahexaenoic Acids on Hepatic Lipogenesis and β-Oxidation in Rats†

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The effects of dietary α-linolenic, eicosapentaenoic and docosahexaenoic acids on the enzyme activities related to hepatic lipogenesis and β-oxidation were compared under constant polysaturated/monounsaturated/saturated fatty acids and n-6/n-3 ratios of dietary fats in rats. Dietary fat containing linoleic acid as the sole polysaturated fatty acid (PUFA) was also given as a control. The concentration of serum triglyceride and phospholipid in the three n-3 PUFA groups was lower than in the linoleic acid group. The hepatic triglyceride concentration was lower and the phospholipid concentration was higher in the three n-3 PUFA groups than in the linoleic acid group. Cytosolic fatty acid synthase (FAS) activity was lower in the n-3 PUFA groups than in the linoleic acid group, the reduction being more predominant in the eicosapentaenoic acid and docosahexaenoic acid groups than in the α-linolenic acid group. The cytosolic activities of the NADPH-generating enzymes, glucose-6-phosphate dehydrogenase (G6PDH) and the malic enzyme, were lower in the three n-3 PUFA groups. The activity of carnitine palmitoyltransferase (CPT) in mitochondria was higher only in the eicosapentaenoic acid group than in the other groups. The activity of Mg2+-dependent phosphatidate phosphohydrolase (PAP) in microsomes and cytosol was lower in the eicosapentaenoic and docosahexaenoic acid groups than in the linoleic acid group, while there was no effect of dietary fats on the activities of diacylglycerol acyltransferase (DGAT) and glycerol-3-phosphate acyltransferase (G3PAT) in microsomes. The CTP: phosphocholine cytidylyltransferase (CT) activity in the homogenate was lower in the n-3 PUFA groups, the reduction being more prominent in the eicosapentaenoic and docosahexaenoic acid groups than in the α-linolenic acid group. The choline kinase (CK) activity in cytosol was lower in the eicosapentaenoic acid group than in the linoleic acid group. These results showed that dietary α-linolenic, eicosapentaenoic and docosahexaenoic acids differently influenced hepatic lipogenesis and the partition of fatty acid into oxidation or glycerolipid synthesis.

Key words: docosahexaenoic acid; eicosapentaenoic acid; α-linolenic acid; lipogenesis; β-oxidation

Introduction

Dietary fish oil containing eicosapentaenoic and docosahexaenoic acids reduces the plasma triglyceride concentration in humans and experimental animals.1,2 It has been reported that the hypotriglyceridemic effect of fish oil may be caused by diminished lipogenesis, increased fatty acid oxidation and reduced VLDL-triglyceride secretion by the liver.2,3 These effects of fish oil have been ascribed to the constituent, eicosapentaenoic acid, but not to docosahexaenoic acid.3,5 We previously reported that dietary docosahexaenoic acid more effectively reduced the liver triglyceride concentration than did eicosapentaenoic or α-linolenic acids.6 These results suggest that docosahexaenoic acid is potentially hypotriglyceridemic. Williams et al. have observed that when docosahexaenoic acid was fed to essential fatty acid-deficient rats, the enzyme activities related to fatty acid synthesis and triglyceride secretion from the liver were diminished.7 However, Willumsen et al. did not observe any hypotriglyceridemic activity with dietary docosahexaenoic acid.8 Wong et al. have shown that adding docosahexaenoic acid to rat hepatocytes decreased triglyceride synthesis as was the case with eicosapentaenoic acid.8 Zhang et al. have observed that, although a perfusion of eicosapentaenoic acid to isolated rat liver suppressed triglyceride secretion, a perfusion of docosahexaenoic acid stimulated triglyceride secretion as was the case with oleic acid.9 Therefore, there is a possibility that docosahexaenoic acid, in comparison with eicosapentaenoic acid, may differently influence lipogenesis, fatty acid oxidation and VLDL secretion in the liver. However, there have been few studies on a quantitative evaluation of the effect of dietary docosa-
hexaenoic and eicosapentaenoic acids on these parameters under physiological conditions.\(^3,\)\(^,\)\(^10\)

In this study, the effect of individual dietary n-3 polyunsaturated fatty acids (PUFA), \(\alpha\)-linolenic, eicosapentaenoic and docosahexaenoic acids on the enzyme activities concerning the synthesis of fatty acid and triglyceride, and fatty acid oxidation in liver was investigated in rats. To minimize the influence of other fatty acids, the ratio of polyunsaturated/monounsaturated/saturated fatty acids was adjusted to the same value in the dietary fats. The ratio of n-6/n-3 PUFA was also adjusted to the same value in the fats containing n-3 PUFA. The control fat contained linoleic acid as the sole PUFA. Enzyme activities concerning phospholipid synthesis were also measured, because the syntheses of triglyceride and phospholipid are closely related to each other and there is a possibility that suppressing triglyceride synthesis could induce the activation of phospholipid synthesis.\(^11,\)\(^12\)

**Materials and Methods**

**Materials.** Eicosapentaenoic acid (purity > 97%) and docosahexaenoic acid (purity > 97%) were isolated from sardine oil and the orbital fat of tuna, respectively, and their ethyl esters were prepared by using an ethanolic hydrogen chloride solution.\(^13\) High-oleic safflower oil and palm oil were provided by Fuji oil (Osaka, Japan). Safflower oil and perilla oil, the seed oil of *Perilla Frutescens* (L.), were products of Rinoru Oil Mills (Nagoya, Japan) and Ohta Oil (Okazaki, Japan), respectively. The other chemicals were obtained from common commercial sources and were of reagent grade.

**Animal and diets.** Male Sprague-Dawley rats (four weeks old) were purchased from Seac Yoshitomi (Fukuoka, Japan) and acclimatized in a room maintained at 20–23°C with a 12-h light-dark cycle. Before starting the experiments, all rats were allowed free access to commercial rat feed (Type NMF, Oriental Yeast Co., Tokyo, Japan). The diets were prepared according to recommendations of the American Institute of Nutrition\(^14\) and contained (in wt%) casein (20), fat (10), AIN-76\(^*\) vitamin mixture (1), AIN-76\(^*\) mineral mixture (3.5), choline bitartrate (0.2), dl-methionine (3), cellulose powder (5), corn starch (15), and sucrose (to make 100). The vitamin and mineral mixtures were purchased from Nihon No- san Kogyo (Tokyo, Japan). The dietary fats were designed to have a constant polyunsaturated:monounsaturated:saturated fatty acid ratio of 1:1:1 and of n-6:n-3 PUFA of 2.3:1. A dietary fat containing linoleic acid as the sole PUFA was also prepared by mixing several vegetable oils. Eicosapentaenoic and docosahexaenoic acids were added as the ethyl esters. The fatty acid composition of each dietary fat is shown in Table I. Ethyl eicosapentaenoate and ethyl docosahexaenoate were mixed daily with the fat mixture, and the blended fats were added to a fat-free diet immediately before providing the diet to the rats. These rats were given only a freshly prepared diet daily from 19:00 for 2 wks. At the end of the study, the rats were killed at 2:00 p.m. by decapitation after 7 h of starvation, and the liver was immediately excised. Blood was collected and the serum was used for a lipid analysis.

**Preparation of liver subcellular fractions.** A piece of liver was homogenized in 6 volumes of a 0.25 M sucrose solution containing 1 mM EDTA in a 10 mM tris-HCl buffer (pH 7.4). After precipitating the nuclei fraction, the supernatant was centrifuged at 10,000 \(\times \) g for 10 min at 4°C to obtain mitochondria. The resulting supernatant was recentrifuged at 125,000 \(\times \) g for 60 min to precipitate microsomes, the remaining supernatant being used as the cytosol fraction. The mitochondrial and microsomal pellets were resuspended in a 0.25 M sucrose solution containing 1 mM EDTA in a 10 mM tris-HCl buffer (pH 7.4).

**Analytical methods.** Liver and plasma lipids were extracted by the method of Folch et al.,\(^15\) the concentration of plasma and liver lipids being measured as previously described.\(^6\) High-density lipoprotein (HDL) cholesterol was analyzed by HDL-C daisie (Daiichi

### Table I. Fatty Acid Composition of the Dietary Fats

<table>
<thead>
<tr>
<th></th>
<th>Linoleic acid (%)</th>
<th>(\alpha)-Linolenic acid (%)</th>
<th>Eicosapentaenoic acid (%)</th>
<th>Docosahexaenoic acid (%)</th>
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<tbody>
<tr>
<td>14:0</td>
<td>0.7</td>
<td>0.5</td>
<td>0.7</td>
<td>0.6</td>
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<tr>
<td>16:0</td>
<td>29.8</td>
<td>29.4</td>
<td>30.2</td>
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<td>18:0</td>
<td>3.2</td>
<td>3.2</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td>18:1</td>
<td>31.7</td>
<td>32.7</td>
<td>33.3</td>
<td>33.6</td>
</tr>
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<td>34.6</td>
<td>23.7</td>
<td>23.9</td>
<td>21.6</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>—</td>
<td>10.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20:4n-6</td>
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<td>—</td>
<td>9.2</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>10.0</td>
</tr>
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<td>SFA</td>
<td>33.7</td>
<td>33.4</td>
<td>33.5</td>
<td>34.6</td>
</tr>
<tr>
<td>MFA</td>
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<td>32.7</td>
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<tr>
<td>n-3PUFA</td>
<td>—</td>
<td>10.4</td>
<td>9.2</td>
<td>10.0</td>
</tr>
</tbody>
</table>

SFA: saturated fatty acid
MFA: monounsaturated fatty acid
PUFA: polyunsaturated fatty acid

\(^*\) AIN-76 vitamin mixture (1), AIN-76 mineral mixture (3.5)
Pure Chemicals, Tokyo, Japan) and protein was assayed by the method of Lowry et al., using bovine serum albumin as a standard.

Assays of enzyme activity. The enzyme activities of fatty acid synthase (FAS), glucose-6-phosphate dehydrogenase (G6PDH), malic enzyme, glyceral-3-phosphate acyltransferase (G3PAT), diacylglycerol acyltransferase (DGAT), phosphatidate phosphohydrolase (PAP), CTP: phosphocholine cytidylyltransferase (CT), choline kinase and carnitine palmityltransferase (CPT) were determined as described earlier.

Statistical analyses. Data were analyzed by Duncan's new multiple-range test, differences being considered significant at \( P < 0.05 \).

Results

Growth performance and liver weight
The body weight, food intake and relative liver weight are shown in Table II. There was no difference in the final body weight among the groups. The food intake of those rats fed on docosahexaenoic acid was slightly but significantly higher than that of those fed on linoleic acid. The relative liver weight was significantly lower in the n-3 PUFA groups than in the linoleic acid group.

Plasma and liver lipids
The concentrations of plasma and liver lipids are shown in Table III. The concentrations of serum and liver triglyceride were lower in the three n-3 PUFA groups than in the linoleic acid group. The concentration of serum phospholipid was significantly lower and that of liver phospholipid was significantly higher in the n-3 PUFA groups than in the linoleic acid group. The concentration of serum total cholesterol was lower in the eicosapentaenoic and docosahexaenoic acid groups than in the linoleic acid group. Docosahexaenoic acid was more effective for lowering the serum cholesterol concentration than eicosapentaenoic acid as previously observed. HDL-cholesterol in the eicosapentaenoic and docosahexaenoic acid groups was significantly lower than in the linoleic acid group, while liver cholesterol was lower in the three n-3 PUFA groups.

Effect of dietary fatty acids on the enzymatic activities related to fatty acid synthesis and oxidation
The activities of hepatic enzymes involved in fatty acid biosynthesis were measured. As shown in Table IV, the cytosolic FAS activity was lower in the n-3 PUFA groups, both eicosapentaenoic and docosahexaenoic acids being more effective than \( \alpha \)-linolenic acid. Dietary n-3 PUFA significantly reduced the activities of the malic enzyme and G6PDH in comparison with the linoleic acid group. Although there was no significant difference, eicosapentaenoic and docosahexaenoic acids tended to be more effective for lowering these enzyme activities.

The activity of CPT, the rate-limiting enzyme of mitochondrial \( \beta \)-oxidation, was measured to evaluate mitochondrial \( \beta \)-oxidation (Table IV). The CPT activity was higher in the eicosapentaenoic acid group than in the other groups.

Effects of dietary fatty acids on the enzymatic activities related to triglyceride and phospholipid syntheses
As shown in Table V, there were no differences

| Table II. Effect of Dietary Polyunsaturated Fatty Acids on the Body Weight Gain, Food Intake and Relative Liver Weight of Rats. |
|---|---|---|---|---|
| Group | Linoleic acid | \( \alpha \)-Linolenic acid | Eicosapentaenoic acid | Docosahexaenoic acid |
| Body weight (g) | | | | |
| Initial | 120 ± 3 | 121 ± 2 | 120 ± 2 | 121 ± 2 |
| Final | 248 ± 3 | 245 ± 5 | 248 ± 2 | 248 ± 4 |
| Food intake (g/day) | | | | |
| 19.5 ±0.7 | 20.0 ±0.4 | 20.4 ±0.4 | 21.2 ±0.4 |
| Relative liver weight (g/100 g of body weight) | | | | |
| 5.37 ±0.10 | 4.87 ±0.22 | 4.52 ±0.22 | 4.64 ±0.09 |

Each value represents the mean ± SE of six rats. Values with different superscript letters are significantly different at \( P < 0.05 \).

| Table III. Effect of Dietary Polyunsaturated Fatty Acids on the Serum and Liver Lipids of Rats |
|---|---|---|---|---|
| Group | Linoleic acid | \( \alpha \)-Linolenic acid | Eicosapentaenoic acid | Docosahexaenoic acid |
| Serum (mg/dl) | | | | |
| Total-C | 96.0 ±6.4 | 81.3 ±5.6 | 74.6 ±5.1 | 58.9 ±2.7 |
| HDL-C | 51.7 ±2.2 | 48.8 ±2.7 | 43.6 ±2.3 | 39.1 ±1.3 |
| Triglyceride | 208 ±42 | 80.4 ±6.1 | 62.2 ±8.3 | 64.7 ±10.0 |
| Phospholipid | 226 ±12 | 173 ±12 | 152 ±9 | 137 ±7 |
| Liver (mg/g) | | | | |
| Cholesterol | 3.68 ±0.33 | 2.91 ±0.12 | 2.76 ±0.19 | 2.82 ±0.18 |
| Triglyceride | 36.3 ±7.1 | 15.7 ±2.9 | 17.6 ±2.6 | 11.0 ±1.4 |
| Phospholipid | 29.4 ±0.4 | 31.9 ±0.6 | 32.1 ±1.0 | 33.4 ±0.4 |

Total-C: total cholesterol, HDL-C: HDL-cholesterol
Each value represents the mean ± SE of six rats. Values with different superscript letters are significantly different at \( P < 0.05 \).
among the four groups in the activity of G3PAT, the first enzyme on the triglyceride biosynthesis pathway. The activity of Mg$^{2+}$-dependent PAP, which controls the branching point in glycerolipid biosynthesis, was significantly lower in the eicosapentaenoic and docosahexaenoic groups than in the linoleic acid group in the cytosolic and microsomal fractions. A similar trend was observed in the activity of Mg$^{2+}$-independent PAP. There was no significant difference in the microsomal DGAT activity among the four groups.

The activity of CT, a rate-limiting enzyme in phosphatidylcholine (PC) biosynthesis, was lower in the three n-3 PUFA groups than in the linoleic acid group when assayed with or without the addition of PC-oleate vesicles. The activity of choline kinase, the first enzyme on the de novo PC biosynthesis pathway, was lower in the eicosapentaenoic acid group than in the linoleic acid group.

**Discussion**

Eicosapentaenoic and docosahexaenoic acids were added as their ethyl esters to the diets, although the other fatty acids were supplemented in their triglyceride form. Several studies have shown that digestion and absorption of these two n-3 PUFA given as an ethyl ester were less effective than when those given as triglyceride. The activities of the malic enzyme, glucose-6-phosphate dehydrogenase, fatty acid synthase and carnitine palmitoyl transferase were measured in the liver cytosol fraction. Carnitine palmitoyl transferase activity was measured in liver mitochondria.

Each value represents the mean±SE of six rats. Values with different superscript letters are significantly different at P<0.05.
same suppressive effect on the activity. The activities of the malic enzyme and G6PDH, NADPH-generating enzymes, were significantly diminished by feeding with n-3 PUFA, and eicosapentaenoic and docosahexaenoic acids again tended to be more effective than α-linolenic acid. The results suggest that eicosapentaenoic and docosahexaenoic acids reduced the rate of fatty acid synthesis more effectively than linoleic and α-linolenic acids.

Although there have been several studies on the suppressive effect of fish oil and eicosapentaenoic acid on the activities of hepatic lipogenic enzymes, little information is available on the effect of dietary docosahexaenoic acid. Williams et al. have reported that when 100 mg of purified methyl docosahexaenoate was given for 3 days to rats fed on an essential fatty acid-deficient diet for 5 weeks, the activities of hepatic FAS, G6PDH and the malic enzyme were lowered, but the effect was similar to that of α-linolenic acid. Willumsen et al. have shown that gastric intubation of eicosapentaenoic acid, when compared with palmitic acid, resulted in the reduction of both the serum triglyceride concentration and of the activities of FAS, G6PDH and acetyl CoA carboxylase in the liver of rats fed on a commercial diet. They did not think that docosahexaenoic acid influenced lipogenesis, because gastric intubation of docosahexaenoic acid did not reduce the serum and hepatic triglyceride concentration. Yang and Williams have also reported that the incorporation of 14C-acetate into fatty acid in hepatocytes isolated from essential fatty acid-deficient rats was suppressed by docosahexaenoic acid. Docosahexaenoic acid tended to be more effective than linoleic, α-linolenic and eicosapentaenoic acids, although they did not calculate the statistical significance. Since the dietary conditions in these studies were quite different from those in our study, the results cannot be simply compared with each other. However, it is reasonable to consider that docosahexaenoic acid had the same activity for lowering fatty acid synthesis as eicosapentaenoic acid had, at least under our comparative dietary conditions.

Although it has been reported that both linoleic and α-linolenic acids suppressed the FAS and G6PDH activities and de novo fatty acid synthesis to the same extent, our results show that α-linolenic acid was more effective for reducing the FAS and G6PDH activities than linoleic acid was. In the previous studies, these fatty acids were given to rats fed on a fat-free diet or an essential fatty acid-adequate, but low-fat diet. Therefore, it is thought that differences in the dietary fat level and fatty acid composition may be causes for the inconsistent results.

It has been reported that dietary fish oil increased hepatic β-oxidation and carnitine palmitoyltransferase activity. Willumsen et al. have shown that dietary eicosapentaenoic acid increased both mitochondrial and peroxisomal β-oxidation, whereas docosahexaenoic acid increased only peroxisomal β-oxidation. Since the activity of carnitine palmitoyltransferase, an indicator of mitochondrial β-oxidation, was increased by the feeding of eicosapentaenoic acid, but not with docosahexaenoic acid, in this study, the result is consistent with that of Willumsen et al. It has been suggested that increased fatty acid oxidation by dietary fish oil was induced by the reduced malonyl CoA concentration following suppressed fatty acid synthesis in the liver. However, only eicosapentaenoic acid stimulated mitochondrial CPT activity, although both eicosapentaenoic and docosahexaenoic acids suppressed FAS activity (Table IV). The differing ability for hepatic β-oxidation between eicosapentaenoic and docosahexaenoic acids suggests that a regulating mechanism other than reduced fatty acid synthesis may exist to regulate mitochondrial β-oxidation. However, the mechanism for the differential effect on β-oxidation between eicosapentaenoic and docosahexaenoic acids remains unsolved.

The activities of three enzymes, G3PAT, PAP and DGAT, on the triglyceride synthesis pathway were measured. It has been reported that the activity of G3PAT, which catalyzes the first step of esterification of triglyceride synthesis, was not affected by dietary n-3 PUFA. Our result is consistent with their observation. In this context, Willumsen et al. have observed a transient reduction of G3PAT activity one day after administering eicosapentaenoic acid, but with prolonged administration, the activity returned to the basal level.

Significant suppression of the soluble and membrane-bound forms of Mg2+-dependent PAP activity was especially found in both the eicosapentaenoic acid and docosahexaenoic acid groups (Table V), although DGAT activity was not influenced by the dietary fats. PAP is thought to be the key enzyme in the regulation of triglyceride biosynthesis. The effect of n-3 PUFA on PAP and DGAT activities is controversial. Several studies have shown that dietary fish oil reduced hepatic PAP activity, whereas others have reported the reduction of DGAT activity. No significant effect on DGAT activity has also been reported from eating a fish oil diet. Although a more detailed study is necessary, these controversial results suggest a possibility that changes in these enzyme activities are secondary to a reduction of fatty acid synthesis by feeding on n-3 PUFA.

The concentration of serum phospholipid was lower in the n-3 PUFA groups, and particularly in the eicosapentaenoic and docosahexaenoic acid groups (Table III). Serum phospholipid is mainly distributed in the HDL fraction which is the major lipoprotein in rats. Since HDL-cholesterol was lower in the n-3 PUFA groups, it is thought that serum phospholipid was decreased concomitantly with the reduction of HDL. In contrast, the liver phospholipid concentration was higher in the n-3 PUFA groups. It has been reported that triglyceride synthesis from radioactive oleate was suppressed, but that phospholipid synthesis was accelerated in cultured hepatocytes from rats fed on fish oil. Therefore, it is thought that diacylglycerol, a common precursor of triglyceride and phospholipid synthesis, is predominantly used as a substrate for phospholipid synthesis with the reduction in triglyceride synthesis by feeding n-3 PUFA. However, our results reveal that
hepatic CT activity was reduced by dietary n-3 PUFA, in particular by eicosapentaenoic and docosahexaenoic acids (Table V). Yamamoto et al.33 and Halminski et al.33 have also observed lower hepatic CT activity by feeding with fish oil. CT is a rate-limiting enzyme of PC synthesis, and the activity was suppressed by an increase in hepatic PC concentration.32 Since the phospholipid concentration in liver was significantly higher in the n-3 PUFA groups, it seems likely that the low CT activity was caused by feed-back inhibition. Yamamoto et al. have previously observed the suppression of CK activity by feeding with fish oil compared with beef tallow.33 Since the CK activity was only lower in the eicosapentaenoic acid group in the present study, the reduction in CK activity by dietary fish oil may be ascribable to eicosapentaenoic acid.

The liver and serum triglyceride concentrations were highly and positively correlated with the fatty acid synthase activity (r=0.76 and 0.77, respectively). Therefore, suppression of fatty acid synthesis seems to be one of the most important factors for determining the triglyceride concentration in liver and serum. However, there have been several studies in which the reduction of hepatic lipogenesis did not induce a decrease in the liver triglyceride concentration. Although liver lipogenesis and the plasma triglyceride concentration were decreased by dietary fish oil, the liver triglyceride concentration was increased,39 or remained unchanged.31 These results suggest that the hepatic triglyceride concentration would not be determined only by fatty acid synthesis. The secretion rate of VLDL-triglyceride from the liver is another major determinant of the liver triglyceride concentration. There is the possibility that a synchronized reduction of hepatic lipogenesis and VLDL secretion would not induce a change in the hepatic triglyceride concentration.

The serum and liver cholesterol concentrations were lower in the n-3 PUFA groups than in the linoleic acid group (Table III). In particular, docosahexaenoic acid was most effective. These results are consistent with those of our previous study in which dietary docosahexaenoic acid significantly lowered the liver and serum cholesterol concentrations in comparison with dietary α-linolenic acid.6 We suggested that the suppression of cholesterol biosynthesis in the liver was one of the causes of this reduction. The results of this present study suggest the possibility that dietary α-linolenic and eicosapentaenoic acids would suppress cholesterol biosynthesis compared with linoleic acid, although less effectively than docosahexaenoic acid.

References