Polyunsaturated Fatty Acids and Atherosclerosis

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The primary cause of coronary heart diseases(CHD) is coronary atherosclerosis, due to lipid-rich lesions in the intima of the coronary arteries. These begin in early life as "fatty streaks" and later form fibrous, often calcified and ulcerated, lesions that narrow the arterial lumen (Table 1)(1). A thrombus, superimposed on the lesions, may precipitate myocardial infarction and sudden death. Abundant evidence supports the conclusion that elevated levels of serum cholesterol and LDL constitute a major risk of atherosclerosis and coronary heart diseases. Postprandial lipemia could influence the process of atherosclerosis. There is growing interest in the process of lipid peroxidation in atherosclerosis. Factors in the vessel wall that directly affect the development of the atherosclerotic process must also be considered. These include the cellular growth factors, without which the atheroclerotic process would probably not develop.

Saturated fatty acids and serum lipids

The principal nutritional factors that affect the level of LDL-cholesterol are the saturated fatty acids with 12 to 16 carbon atoms and dietary cholesterol. These two

Table 1. Concentration of esterified cholesterol in grossly normal and atherosclerotic aortic intima in Japanese

Age(yr)	Esterified cholesterol(mg/g dry wt)			
	0~20	21~40	41~60	>61
Normal	4.5(7)	11.1(8)	23.0(14)	19.3(13)
Fatty Streak	19.5(4)	51.2(4)	59.3(15)	47.9(13)
Diffuse intimal thickening	–	9.4(3)	27.5(5)	30.3(7)
Fibrous plaque	–	–	58.2(3)	36.5(4)
Fibrofatty plaque	–	–	68.1(4)	174 (4)
Atheroma	–	54.6(3)	123 (11)	140 (17)
Complicated	–	–	94.4(6)	83.8(10)

Figures in the parenthesis show number of samples

Table 2. Effects of different saturated fatty acid fats on fractional catabolic rate of [125-I] labeled LDL in hamsters fed diets with cholesterol

Group	Fractional catabolic rate
	h^{-1}
Lauric acid fat	0.082^{a}
Myristic acid fat	0.080^{a}
Palmitic acid fat	0.076^{a}
Stearic acid fat	0.199^{b}

Values are mean for 4 animals per group
$^{ab}p<0.05$

can increase the level of LDL-cholesterol. Keys et al.(2) and Hegsted et al.(3) developed formulas for predicting cholesterol levels based upon dietary changes. In these cases they found that stearic acid did not fit the formula. We found that hamsters fed stearic acid-containing diet, compared to other saturated fatty acids, resulted in greater fractional catabolic rate of [125-I]-labeled homologous LDL(Table 2)(4).

n-6 PUFA and serum lipids

The major fatty acids of the diet in quantitative terms are unsaturated fatty acids. This category of fatty acids includes n-6 PUFA, n-3 PUFA and monounsaturates. According to the equations developed by Keys et al., saturates increase cholesterol levels twice as much as linoleic acid lowers them, both relative to carbohyrates. When the literature refers to "PUFA," unless otherwise indicated, this usually means linoleic acid. In the United States, Australia and the United Kingdom, the changing balance of PUFA to saturated fatty acids correlates better with the fall in CHD than do changes in total fat or saturated fat intake. On the other hand, a higher consumption may increase risk for some cancers, promote LDL oxidation

Table 3. Role of n-6 PUFA in human health

Beneficial effects
(a) lower the blood cholesterol and the blood pressure
(b) protect against cardiac arrhythmias and coronary atherosclerosis
Concern about a high intake of linoleic acid(>10%)
(a) may increase certain types of human cancer (breast, colon, prostate)
(b) may promote oxidation of LDL in the arterial wall

within the arterial wall, and possibly raise the risk for coronary thrombosis(Table 3). Until a better assessment has been made of the balance between harm and benefit, prudence suggest that intake of linoleic acid not exceed current levels in those countries.

n-3 PUFA and serum lipids

The early epidemiological observations in the Greenland Eskimos and in Japanese fisher-folk versus farmers strongly suggested that populations that consume more n-3 fatty acids from fish, seal, and other sea life had much lower mortality rates from CHD. The important biologically active components of fish oil are n-3 fatty acids. In the area of human lipoprotein metabolish, it is clear that their primary effect is on the triglyceride(TG), not Cholesterol. This should not be taken to mean fish oils will have no effect on CHD, however, because they also affect a myriad of potentially atherogenic processes.

EPA and DHA are the major n-3 fatty acids in fish oils and α-linolenic acid are the precursors for the synthesis of these fatty acids. α-Linolenic acid in the diet dose not have the same biological effects as EPA and DHA from fish oils. We found that the concentration of plasma TG was lower in rats fed EPA than in those fed DHA and α-linolenic acid(5). In addition, both EPA and DHA decreased hepatic TG compared with linolenic acid, but this effect was more pronounced in the DHA group (Table 4). There are rate-limiting steps, the first being at the site of action of the δ6-desaturase enzyme, so that the provision of large quantities of α-linolenic acid in the diet may not necessarily mean similarly large quantities of EPA and DHA. Since Eskimos eat a diet from seals, we have examined hypotriglyceridemic activity of seal-derived TG(6). EPA and DHA were distributed mainly in the sn-1 and 3 positions of seal and in the sn-2 position of fish oil(Table 5). The structural distribution of EPA and DHA in lymph TG of rats given seal or fish oils was similar to the distribution in their original oils. Seal oil more effectively reduced plasma and liver TG than fish oil(Table 6). The results suggest that the different intramolecular distribution of EPA and DHA in dietary fat differently modulate lipid metabolism.

PUFA and atherosclerosis

There is ample epidemiological evidence suggesting

Table 4. Plasma and liver lipids concentration in rats fed α-linolenic acid, EPA and DHA

Group	Plasma		Liver	
	Cholesterol	Triglyceride	Cholesterol	Triglyceride
	mmol/L		μmol/g wet wt	
α-Linolenic	2.09[a]	1.29[ab]	8.22[a]	23.2[a]
EPA	1.84[ab]	0.853[b]	7.63[a]	15.3[ab]
DHA	1.47[b]	1.57[a]	6.16[b]	11.9[b]

Values are means of 6 rats
[ab]Within a column, $p<0.05$

Table 5. Positional distribution of EPA and DHA in oil and lymph triglyceride

Fatty acid	Administered oil				Lymph triglyceride			
	Fish oil		Seal oil		Fish oil		Seal oil	
	sn-2	sn-1(3)	sn-2	sn-1(3)	sn-2	sn-1(3)	sn-2	sn-1(3)
EPA	20.7	17.3	2.1	20.3	11.0	18.1	3.5	15.4
DHA	25.0	8.5	1.7	20.9	16.2	10.3	4.3	16.4

Values are means of 5~6 rats

Table 6. Plasma and liver lipid concentration in rats fed seal or fish oil

	Groups		
	Control	*Fish oil*	*Seal oil*
Plasma(mg/dl)			
Total cholesterol	75.0	62.4	65.3
Triglyceride	159[a]	111[ab]	72.3[b]
Liver(mg/g liver)			
Total cholesterol	2.69	3.04	2.59
Triglyceride	19.0[a]	16.0[ab]	11.6[b]

Values are means of 5~6 rats
[ab]$p<0.05$

that n-3 fatty acids protect against atherogenesis. However, the many experimental studies that have evaluated the effects of fish oil on the development of atherosclerosis have generated ambiguous results, possibly as a result of differences in species(nonhuman primates, swine, rabbits, Japanese quail, mouse), dose of EPA(7.5 to 330mg/kg body weight per day), type of studied arteries (aorta, coronary arteries, pulmonary artery, iliac artery), duration of the study(2wk-3yer) or the method used to evaluate the effects(percentage of macroscopically visible lesions, luminal encroachment, and/or aortic lipid). A trial published in USA showed no evidence for a beneficial effect of high doses of n-3 fatty acids on restenosis in patients(7). It should be recognized, however, that atherogenesis and restenosis are different pathological processes.

Parks et al.(1990) measured the extent of coronary atherosclerosis in African green monkeys fed dietary cholesterol. The authors concluded that the potentially antiatherogenic effects of dietary fish oil included its ability to decrease the concentration. size, cholesterol ester content, and melting point temperature of plasma LDL which was altered in fatty acid composition after fish oil. Davis et al.(1987) showed that menhanden oil incorporated into an atherogenic diet inhibited atherosclerotic plaque development in rhesus monkeys, although plasma lipid levels were roughly similar to coconut oil-incorporated diet. Other mechanisms, therefore, have been postulated for antiatherogenic affect of fish oil. Fish oils apparently have a direct effect to prevent the growth of the atherosclerotic plaque with the inhibition of cellular growth factor. In addition, n-3 fatty acids may have an anti-inflammatory action in the blood vessel wall. Indeed our experiment showed that dietary EPA or DHA were incorporated into platelet and aorta and modified PGI_2/TXA_2 ratio and prevented con Adependent proliferation of lymphocytes in experimental animals(5,6). Further research to elucidate an individual role of EPA and DHA in Atherosclerosis are needed.

Table 7. Recommended dietary allowance for Japanese (5th Revision, 1995)

Level of fat	20-25 en%
Quality of fat	S : M : P=1 : 1.5 : 1
	n-6/n-3=4
Cholesterol	less than 300mg/day

Interaction of dietary PUFA to proteins

Dietary proteins, particularly casein and soybean protein, also influences metabolism of PUFA, serum lipid levels and development of atherosclerosis. Our results showed that soybean protein, compared to casein, suppressed atherosclerotic development in apo E deficient mice that are susceptible to atherosclerosis(unpublished observation). In addition, the effects of dietary protein and fats(perilla oil or safflower oil) on the fatty acid composition and prostacyclin production in aorta were studied in stroke-prone spontaneous rats(8). The results indicated a significant role of dietary protein in the regulation of PUFA and eicosanoid production.

Lipid consumption advice in Japan

According to Recommended Dietary Allowance, it is desirable to include fat in the diet at the extent of 20-25% of total calories with ratios of saturated : monounsaturated : polyunsaturated fatty acids=1 : 1.5 : 1(9). A ratio of n-6 to n-3 PUFA is desirable to be 4 : 1(Table 7).

The best dietary advice for most healthy people should be moderation, balance and variety.

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