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The Long-Term Effect of Eicosapentaenoic Acid on Serum Levels of Lipoprotein (a) and Lipids in Patients with Vascular Disease

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The effects of eicosapentaenoic acid (EPA) on serum lipoprotein (a) (Lp(a)) and other lipid levels in patients with vascular disease were examined. The serum levels of Lp(a), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were measured in 24 patients with vascular disease. An elevated serum Lp(a) level (39±22 mg/dl) was noted in 9 patients, elevated total cholesterol level (263±31 mg/dl) in 12 patients, elevated triglyceride level (240±98 mg/dl) in 10 patients and elevated LDL level (651±88 mg/dl) in 6 patients before administration of EPA. EPA (1,800 mg/day) was given to these patients for long periods ranging from 6 to 24 months. The serum levels of Lp(a), TC, TG and LDL were lowered significantly ($p<0.05$) after EPA administration for 12 and 18 months, for 6, 12, 18 and 24 months, for 18 months and for 12 and 18 months, respectively. These findings indicated that long-term administration of EPA may lower Lp(a) and serum lipids, which is beneficial for patients with various arterial diseases in terms of preventing progression of the disease. ***J Atheroscler Thromb, 1996; 2: 107-109.***

Key words: Atherosclerosis, Oral Administration, Total cholesterol, Triglyceride

Eicosapentaenoic acid (EPA) has been suggested to prevent arterial thrombosis and development of atherosclerosis by altering lipid metabolism in addition to its known antiplatelet effect (1). Lipoprotein (a) (Lp(a)), described by Berg in 1963, is a variant of low-density lipoprotein (LDL), which has been reported to be correlated with an increased risk of atherosclerotic vascular disease (2). A high concentration of Lp(a) in plasma has been reported to be an independent risk factor for acute myocardial infarction and to be increased in patients with peripheral vascular diseases (3). Some studies have suggested that the Lp(a) level is under tight genetic control and is not influenced by diet (4). However, nicotinic acid and stanozolol have been reported to lower the Lp (a) level (5, 6).

We examined whether the long-term administration of EPA influenced the serum levels of Lp (a) and other lipids in patients with vascular disease. In this study, the serum levels of Lp (a), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were measured in patients with arteriosclerosis obliterans (ASO), Buerger's disease (TAO) and abdominal aortic aneurysm (AAA) before and after administration of EPA.

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Methods

The subjects were 24 patients with vascular disease who visited our clinic from February 1991 to March 1992. The 24 patients were comprised of 21 men and 3 women aged 38-75 years. Sixteen patients with ASO, 6 patients with TAO and 2 patients with AAA received oral administration of 1,800 mg/day of EPA (Epadel, Mochida Pharmaceutical Co., Tokyo, Japan). Informed consent was obtained from all patients before administration of EPA. The serum levels of Lp(a) and various lipid parameters including TC, TG, LDL and VLDL were measured before and 6, 12, 18 and 24 months after the administration of EPA. Blood samples were obtained under strict fasting and serum was obtained by centrifugation of the blood at 1,200×g for 5 min. The determination of Lp(a) was performed in the Biochemical

Laboratory (Sumitomo Metal Bio-Science, Inc., Tokyo, Japan) by enzyme immunoassay (7). A Tint Elisa Lp(a) determination kit (Biopool AB, Umea, Sweden) was used. The principle of the ELISA is based on the sandwich technique in which two monoclonal antibodies react with different antigenic determinations on the apo(a) molecule. Blood Lp(a) level was diagnosed as elevated when determined to be above 20 mg/dl. Measurement of LDL and VLDL was performed by turbidometric assay using sodium heparin. The values of blood lipid levels were diagnosed as elevated when TC, TG, LDL and VLDL were above 221, 151, 571 and 410, respectively. Statistical analysis was performed using the paired Wilcoxon test to compare pre- and post-treatment values.

Results

Of the 24 patients studied, an elevated serum Lp(a) level of more than 20 mg/dl (39±22 mg/dl) was noted in 9 patients (7 in ASO, 1 in TAO and 1 in AAA), elevated TC level of more than 220 mg/dl (263±31 mg/dl) in 12 patients (9 in ASO and 3 in TAO), elevated TG level of more than 150 mg/dl (240±98 mg/dl) in 10 patients (7 in ASO, 2 in TAO and 1 in AAA) and elevated LDL level of more than 570 mg/dl (651±88 mg/dl) in 6 patients (5 in ASO, 1 in TAO) before administration of EPA. The levels of VLDL were within the normal limit in all patients. EPA (1,800 mg/day) was given to these patients for 24 months and the data from these patients were analyzed. The serum level of Lp(a) in the patients with elevated Lp(a) levels before EPA administration were lowered significantly ($p<0.05$) after administration for 12 and 18 months. The levels of Lp(a) in patients in which it was initially normal did not change significantly (Fig. 1). The serum level of TC in patients with elevated TC level was lowered significantly after administration of EPA for 6, 12, 18 and 24 months (Fig. 2). The TG level in patients in which it was elevated before administration was lowered significantly after EPA administration for 18 months (Fig. 3). In the patients with an elevated LDL level before treatment, the LDL level was lowered after administration of EPA for 12 and 18 months (Fig. 4). In all patients in the present study, no marked side effects such as liver dysfunction were seen after long-term administration of EPA.

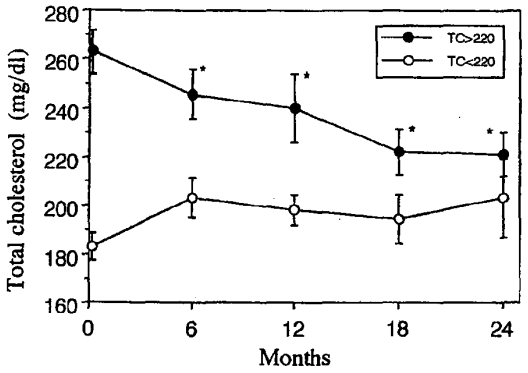

Fig. 2. Effects of administration of EPA on serum total cholesterol (TC) levels. Serum level of TC was measured during EPA treatment. Patients with pretreatment serum levels higher than the normal range (closed circles), and those with normal pretreatment serum levels (open circles). Asterisks denote significant differences ($p<0.05$) from the pretreatment values.

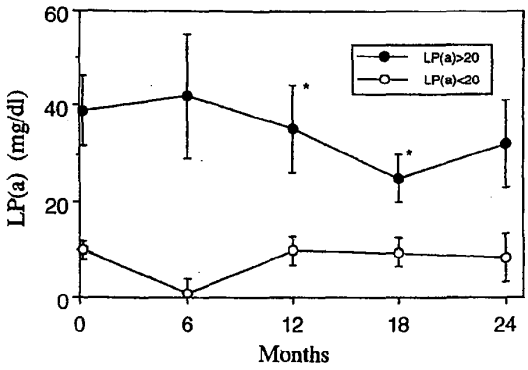

Fig. 1. Effects of administration of EPA on serum Lp(a) levels. Serum level of Lp (a) was measured during EPA treatment. Patients with pretreatment serum levels higher than the normal range (closed circles), and those with normal pretreatment serum levels (open circles). Each value is the mean±SE. Asterisks denote significant differences ($p<0.05$) from the pretreatment values.

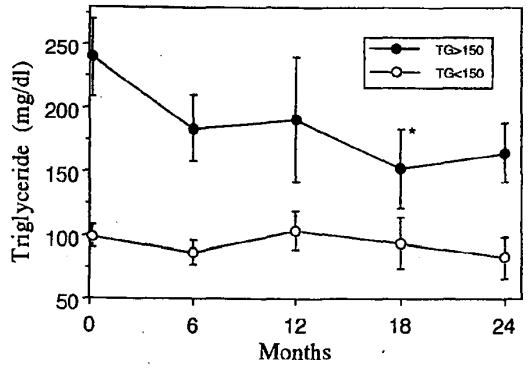

Fig. 3. Effects of administration of EPA on serum total triglyceride (TG) levels. Serum level of TG was measured during EPA treatment. Patients with pretreatment serum levels higher than the normal range (closed circles), and those with normal pretreatment serum levels (open circles). Asterisks denote significant differences ($p<0.05$) from the pretreatment values.

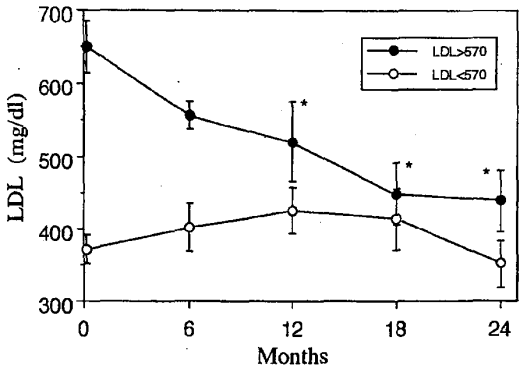

Fig. 4. Effects of administration of EPA on serum low-density lipoprotein (LDL) levels. Serum level of LDL was measured during EPA treatment. Patients with pretreatment serum levels higher than the normal range (closed circles), and those with normal pretreatment serum levels (open circles). Asterisks denote significant differences ($p<0.05$) from the pretreatment values.

Discussion

Lp(a) has been assumed to be an additional risk factor for atherosclerotic diseases (8). Therefore, reduction of the serum concentration of Lp(a) would be of great clinical interest. Recently, the effects of several drugs to reduce the effect of Lp(a) have been studied. Carlson *et al.* reported the pronounced Lp(a)-lowering effect of nicotinic acid in hyperlipidemic subjects (5). Vessby *et al.* studied the effects of cholestyramine (9) and Schmidt *et al.* investigated the effects of n-3 polyunsaturated fatty acids on Lp(a) (10). In this latter study, patients were given n-3 polyunsaturated fatty acids including EPA and DHA for 6 or 12 weeks, but no effect on Lp(a) was observed. In the present study, capsules containing 100% pure eicosapentaenoic acid were used. When analyzing the data, patients were divided into two groups according to the Lp(a) level before EPA administration. The level of Lp(a) in patients with a high level before administration decreased after 12 and 18 months of EPA administration. The mechanism of synthesis and degradation of Lp(a) is not clear at present, and there is no good explanation for the observed effect of EPA. Since Lp(a) contains an LDL component (apo-B) linked to apo(a) by a single disulfide bridge (11), the significant reduction of LDL after administration for 12 and 18 months is of interest. Intake of EPA might reduce hepatic synthesis of low-density lipoproteins and decrease the production of Lp(a) in the liver. We also studied the changes in the levels of TC, TG and LDL. The serum levels of TC, TG and LDL in the patients in which these levels were high before treatment were lowered significantly after administration of EPA for 6, 12, 18 and 24 months, for 18 months and for 12 and 18 months, respectively. Harris *et al.* reported that intake of n-3 fatty acids produced persistent reductions in TG levels, but not in TC or LDL levels (12), and Gries *et al.* reported that n-3 fatty acids could reduce the TG level after 6 months of treatment (13). The effect of EPA on TG in the present study was compatible with the results of these previous studies. However, the long-term effects of administration of highly purified EPA for more than 1 year have not been reported. The present study showed that the long-term administration of EPA reduced not only the Lp(a) level, but also the serum levels of TC, TG and LDL.

In conclusion, these findings indicate that long-term administration of EPA may lower the levels of Lp(a) and serum lipids such as triglyceride and LDL, and that this treatment is safe and beneficial for patients with various arterial diseases in terms of preventing progression of the disease.

References

(1) Needleman P and Raz A: Triene prostaglandins; prostacycline and thromboxane biosynthesis and unique biological properties. Proc Natl Acad Sci USA, 76: 944-948, 1979
(2) Berg K: A new serum system in man. - The LP system. Acta Pathol Microbiol Scand, 59: 369-382, 1963
(3) Widmann MD and Sumpio BE: Lipoprotein(a); A risk factor for peripheral vascular disease. Ann Vasc Surg, 7: 446-451, 1993
(4) Utermann G, Menzel HJ, and Kraft HG: Lp(a) glycoprotein phenotypes; Inheritance and relation to Lp(a)-lipoprotein concentrations in plasma, J Clin Invest. 80: 458-465, 1987
(5) Carlson LA, Hamsten A, and Asplund A: Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. J Intern Med, 226: 271-276, 1989
(6) Thompson PD, Cullinane EM, and Sady SP: Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. JAMA, 261: 1165-1168, 1989
(7) Abe A, Maeda S, and Makino K: Enzyme-linked immunosorbent assay of lipoprotein(a) in serum and cord blood. Clin Chim Acta, 177: 31-40, 1988
(8) Rhoads GG, Dahlen G, and Berg K: Lp(a) lipoprotein as a risk factor for myocardial infarction. JAMA, 256: 2540-2544, 1986
(9) Vessby B and Kostner G: Diverging effects of cholestyramine on apoprotein B and lipoprotein Lp(a), Atherosclerosis, 44: 61-71, 1982
(10) Schmidt EB, Klausen IC, and Kristensen SD: The effect of n-3 polyunsaturated fatty acids on Lp(a). Clin Chim Acta, 198: 271-277, 1991
(11) Joseph L: Lipoprotein (a) A unique risk factor for atherothrombotic disease. Arteriosclerosis, 10: 672-679, 1990
(12) Harris WS, Windsor SL, and Dujovne CA: Effect of four doses of n-3 fatty acids given to hyperlipidemic patients for six months. J Ame Coll Nutr, 10: 220-227, 1991
(13) Gries A, Malle E, Wurm H, and Kostner GM: Influence of dietary fish oils on plasma Lp(a) levels. Thromb Res, 58: 667-668, 1990