Fish Oil–Derived Fatty Acids, Docosahexaenoic Acid and Docosapentaenoic Acid, and the Risk of Acute Coronary Events

The Kuopio Ischaemic Heart Disease Risk Factor Study

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Background—Previous findings concerning the serum levels of fish-derived (n-3) fatty acids and coronary heart disease are inconsistent. The purpose of this study was to investigate the association between the serum n-3 end-product fatty acids docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid and the risk of acute coronary events in middle-aged men.

Methods and Results—We studied this association in the Kuopio Ischaemic Heart Disease Risk Factor Study, a prospective population study in Eastern Finland. Subjects were randomly selected and included 1871 men aged 42 to 60 years who had no clinical coronary heart disease at baseline examination. A total of 194 men had a fatal or nonfatal acute coronary event during follow-up. In a Cox proportional hazards’ model adjusting for other risk factors, men in the highest fifth of the proportion of serum DHA and DPA in all fatty acids had a 44% reduced risk (P=0.014) of acute coronary events compared with men in the lowest fifth. Men in the highest fifth of DHA and DPA who had a low hair content of mercury (<2.0 μg/g) had a 67% reduced risk (P=0.016) of acute coronary events compared with men in the lowest fifth who had a high hair content of mercury (>2.0 μg/g). There was no association between proportion of eicosapentaenoic acid and the risk of acute coronary events.

Conclusions—Our data provide further confirmation for the concept that fish oil–derived fatty acids reduce the risk of acute coronary events. However, a high mercury content in fish could attenuate this protective effect. (Circulation. 2000;102:2677-2679.)

Key Words: epidemiology ■ fatty acids ■ myocardial infarction ■ nutrition ■ mercury

Nutrition plays an important role in the development of coronary heart disease (CHD). The low incidence of CHD in Greenland Eskimos was proposed to be due to the peculiar fatty acid composition of their diet. High dietary fish intake or high circulating or tissue levels of fish-derived fatty acids has been associated with a reduced risk of CHD in some, but not in all, studies. Previous observations have suggested that a high mercury intake may increase the risk of myocardial infarction and accelerate atherosclerosis. A high mercury content in fish could counteract the protective metabolic effects of the fatty acids in fish. The purpose of this study was to investigate the association between the serum n-3 end-product fatty acids docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) and the risk of acute coronary events in middle-aged men from eastern Finland and to test how the hair content of mercury modifies this association.

Methods

The Kuopio Ischaemic Heart Disease Risk Factor Study is an ongoing, prospective, population-based cohort study investigating risk factors for cardiovascular diseases, atherosclerosis, and related outcomes in middle-aged men from Eastern Finland. The study protocol was approved by the Research Ethics Committee of the University of Kuopio. Each subject gave written, informed consent to participate in the study.

The province of Kuopio participated in the multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) project FINMONICA (http://www.ktl.fi/publications/monica). The diagnostic classification applied in this study was described previously. The average follow-up time for the cohort was 10 years (from March 1984 to December 1997). Of the total of 194 coronary events in the 1871 subjects, 100 were definite and 60 were probable acute myocardial infarctions and 34 were typical episodes of acute chest pain. Serum fatty acids were measured with capillary gas chromatography (Hewlett Packard 5890 Series II with flame ionization detector and 7673 autosampler). The percent proportion of the sum of DHA and DPA in all fatty acids was calculated.
An assessment of covariates was performed as described previously. The subjects were classified using quintiles of their serum DHA+DPA proportion of all fatty acids. Baseline characteristics of the cohort, divided by DHA+DPA quintiles, were compared by ANOVA. Associations of risk factors with the risk of acute coronary events were analyzed using Cox proportional hazards’ models (SPSS Inc). Relative hazards (risks), adjusted for risk factors, were estimated as antilogarithms of coefficients for independent variables. The confidence intervals (CI) were estimated on the basis of the assumption of asymptotic normality of estimates. All statistical tests were 2-tailed.

Results

The mean proportion (%) of serum DHA+DPA of all fatty acids was 3.01±0.79% (range, 1.39% to 7.51%). We categorized the subjects into fifths of this proportion (<2.38%, 2.38% to 2.73%, 2.74% to 3.07%, 3.08% to 3.58%, and >3.58%) and compared the lowest fifth with the others. The characteristics of the subjects in these fifths are shown in the Table. Men in the highest fifth of the proportion of serum DHA+DPA had an 8.9% higher serum HDL cholesterol (P<0.001 for trend), 13.2% lower serum fasting insulin level (P=0.014 for trend), and 16.4% lower ADP-induced platelet aggregability (P=0.018 for trend) than men in the lowest fifth.

In a Cox proportional hazards’ model adjusting for age, examination years, body mass index, maximal oxygen uptake, hair mercury content, serum ferritin, serum LDL cholesterol, systolic blood pressure, serum insulin, ADP-induced platelet aggregation, socioeconomic status, ischemic findings in exercise test, smoking, place of residence, and dietary energy intake, men in the highest fifth of the proportion of serum DHA+DPA had a 44% (95% CI, 11% to 65%; P=0.014) reduced risk of acute coronary events compared with men in the lowest fifth. The risk was significantly lower among men in the 4 highest fifths than among men in the lowest fifth (P=0.010 for linear trend over fifths). No statistically significant association existed between serum EPA proportion and the risk of acute coronary events.

The mean hair content of mercury was 1.91 μg/g and ranged from none to 15.67 μg/g. In a Cox proportional hazards’ model adjusting for cardiovascular risk factors, men in the 2 lowest thirds of hair content of mercury (0 to 2.0 μg/g) who were also in the highest fifth of the proportion of serum DHA+DPA had a 67% (95% CI, 19% to 87%; P=0.016) reduced risk of acute coronary events compared with men in the highest third of hair mercury content who were also in the lowest fifth of the proportion of serum DHA+DPA (Figure).

Discussion

This prospective population-based study shows that a high proportion of the fish-derived fatty acids DHA and DPA in serum is associated with a decreased risk of acute coronary events in middle-aged men from eastern Finland. This association was strong and independent of other risk factors. Previous findings concerning a high fish intake and CHD are inconsistent, or the protective effect was found only for fatty fish. Cardiovascular diseases are common in Finland, especially in men, despite a high fish consumption. The mercury content in Finnish lakes is high, and high mercury concentrations have been measured in fish from Finnish lakes. We showed that a high intake of mercury from non-fatty freshwater fish and the consequent accumulation of

| Main Characteristics of Subjects According to Quintile of the Proportion of Serum Concentration of DHA+DPA of All Fatty Acids |
|---|---|---|---|---|---|---|
| Quintiles of Serum DHA+DPA | <2.38% | 2.38% to 2.73% | 2.74% to 3.07% | 3.08% to 3.58% | >3.58% | P for Heterogeneity |
| Age, y | 52.3 | 52.4 | 52.2 | 52.8 | 52.4 | 0.521 |
| Body mass index, kg/m² | 26.5 | 26.7 | 26.7 | 27.0 | 26.9 | 0.283 |
| Dietary energy intake, MJ/d | 11.4 | 11.1 | 10.8 | 10.6 | 10.2 | <0.001 |
| Hair mercury content, μg/g | 1.16 | 1.66 | 1.82 | 2.34 | 2.57 | <0.001 |
| Ischemic findings in exercise ECG, % | 21.9 | 15.2 | 18.7 | 15.5 | 17.4 | 0.110 |
| Maximal oxygen uptake, mL · kg⁻¹ · min⁻¹ | 31.5 | 32.4 | 31.9 | 32.3 | 32.5 | 0.277 |
| Place of residence, rural vs other, % | 38 | 29 | 24 | 28 | 20 | <0.001 |
| ADP-induced platelet aggregation, mV | 16.3 | 14.7 | 14.9 | 13.7 | 14.0 | 0.018 |
| Systolic blood pressure, mm Hg | 135.3 | 134.7 | 134.2 | 134.5 | 133.4 | 0.656 |
| Serum total cholesterol, mmol/L | 5.82 | 5.97 | 5.84 | 5.82 | 5.85 | 0.305 |
| Serum HDL cholesterol, mmol/L | 1.23 | 1.27 | 1.31 | 1.34 | 1.34 | <0.001 |
| Serum LDL cholesterol, mmol/L | 3.88 | 4.10 | 3.97 | 4.00 | 4.06 | 0.029 |
| Serum ferritin, μg/L | 152 | 153 | 161 | 183 | 184 | 0.002 |
| Fasting serum insulin, mU/L | 12.0 | 11.6 | 10.7 | 10.9 | 10.6 | 0.014 |
| Smoking, % | 33.6 | 34.2 | 31.0 | 28.3 | 22.2 | <0.001 |
| Socioeconomic status, *0–19 | 8.5 | 8.6 | 7.9 | 7.9 | 7.0 | 0.002 |

Values are mean unless otherwise indicated.

*Summary index (income, education, occupation, occupational prestige, material standard of living, and housing conditions).
mercury in the body are associated with an excess risk of myocardial infarction in men in eastern Finland. Mercury compounds could promote the peroxidation of unsaturated fatty acids such as DHA and DPA. However, mercury forms an insoluble complex with selenium, binding selenium in an inactive form that cannot serve as a cofactor for glutathione peroxidase and has a very high affinity to sulfhydryl groups. Therefore, mercury could inhibit important antioxidative mechanisms in humans. Fish and fish products are the dominant source of methyl mercury in food. The CHD risk–increasing effect of mercury can explain the inconsistency of results in the numerous studies of the association between fish intake or circulating levels of fish-derived fatty acids and CHD.

In the Physicians’ Health Study, concentrations of DHA and EPA in plasma cholesterol esters and phospholipids did not differ between subjects with CHD and controls. In the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer (EURAMIC), there was no association between the DHA in adipose tissue and the risk of myocardial infarction. However, the DPA synthesized from EPA was not measured. In a randomized dietary intervention trial in patients after myocardial infarction, there was a significant reduction in cardiovascular mortality in those who received supplements of n-3 polyunsaturated fatty acids (1 g of daily DHA + EPA). Our results provide further confirmation of the concept that fatty acids from fish reduce the risk of acute coronary events. However, the mercury in fish could attenuate this protective effect.

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References

12. Lakka TA, Venaläinen JM, Raumaara R, et al. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myo-
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