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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1060 – 1064
Metabolism Clinical and Experimental
www.elsevier.com/locate/metabol

Fish consumption and early atherosclerosis in middle-aged men

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Received 21 November 2006; accepted 28 March 2007

Abstract

To investigate the association between fish consumption and early atherosclerosis, we analyzed the relationship between fish consumption and average intima-media thickness (AveIMT) by carotid ultrasound in middle-aged Japanese men. Participants were 250 randomly selected, community-based Japanese men aged 40 to 49 years without a prior history of cardiovascular disease. AveIMT was calculated from the mean of 1-cm lengths of both the right and the left carotid arteries at 8 locations. A lifestyle survey was carried out using a self-administered questionnaire including the frequency of fish intake. There were 147 men in the fewer than 4 times per week fish consumption group and 103 men in the 4 or more times per week group. The mean AveIMT was significantly higher in the low fish consumption group than in the high fish consumption group (0.623 ± 0.068 vs 0.605 ± 0.065 mm, P = .03). After adjustment for age, waist circumference, pack-years of smoking, alcohol consumption, diabetes, and lipid-lowering medications, the significant difference in the AveIMT between the 2 groups remained. However, after further adjustment for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and C-reactive protein in the model, the significant difference disappeared. Fish consumption may be protective against early atherosclerosis in middle-aged men, probably through its beneficial effects on inflammation.

1. Introduction

A large number of epidemiologic studies have found beneficial effects of fish intake on coronary heart disease events, coronary heart disease death, sudden cardiac death, or all-cause mortality [1-11]. The proposed potential mechanisms by which eating fish may reduce risk for cardiovascular disease include an antiatherosclerotic effect of n-3 polyunsaturated fatty acids (PUFAs) [12].

The intima-media complex in the carotid arteries starts to thicken early in the atherosclerosis process, although plaques are seen infrequently [13]. Thus, ultrasonic evaluation of intima-media thickness (IMT) is one method of assessing the development of early atherosclerosis. According to a recent meta-analysis by Balk et al [14], data concerning fish oil consumption and carotid atherosclerosis are inconclusive. Thus, we analyzed the relationship between fish consumption and IMT in middle-aged Japanese men randomly selected from a community.

2. Methods

2.1. Study population

Participants were men aged 40 to 49 years from Kusatsu City, Shiga Prefecture, Japan, randomly selected using the information from the Basic Residents' Register, which provides each resident's name, birth date, address, name of a family representative, whether or not on an electoral list, type of health insurance, and other details. All Japanese nationals are required to register by law. The register can be perused for research purposes; however, only information on name, birth date, address, and name of a family representative was given to us from the local authority. Exclusion criteria included the presence of (1) clinical cardiovascular disease, (2) type 1 diabetes mellitus, (3) cancer except skin

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doi:10.1016/j.metabol.2007.03.014

cancer in the past 2 years, (4) renal failure, and (5) genetic familial hyperlipidemia. From May 2001 to November 2003, randomly selected men from the register were contacted consecutively via telephone by use of a random digits table. The rate of participation was 49%. Informed consent was obtained from all eligible 250 participants [15]. The Institutional Review Board of Shiga University Medical Science approved this study.

2.2. Baseline and biochemical examinations

Blood pressure was measured in the right arm of the seated participants after the participants were seated quietly for 5 minutes, using an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan). The average of 2 measurements was used. Body weight and height were measured while the participants were wearing light clothing on stocking feet. Waist circumference was measured with a tape measure at the level of the umbilicus, while the participants were standing, wearing an undergarment, and at the end of exhalation. Venipuncture was performed early in the clinic visit after a 12-hour fast. Plasma or serum samples were prepared and frozen at −80°C. The samples were shipped on dry ice to the Heinz Laboratory, University of Pittsburgh (Pittsburgh, PA). Serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose, and C-reactive protein (CRP) concentrations were measured as previously described [16]. An insulin resistance index, the homeostasis model assessment of insulin resistance (HOMA-IR), was obtained by the formula insulin (μU/mL) × fasting blood glucose (mg/dL)/405 [17]. Diabetes was defined as a fasting serum glucose concentration of 126 mg/dL or greater and/or being on medications for diabetes.

A lifestyle survey was carried out by using a self-administered questionnaire, which asked about the usual average consumption of food items. Fish consumption was queried using 8 categories: more than once per day, once per day, 4 to 5 times per week, 2 to 3 times per week, once per week, 1 to 3 times per month, fewer than once per month, and rare or never. Current smoking was defined as smoking cigarettes over the last month. Pack-years were calculated as years of smoking multiplied by the number of cigarettes per day divided by 20. Alcohol drinkers were defined as drinking alcohol 2 days per week or more. Ethanol consumption per day was estimated assuming that concentrations of alcohol were 5% for beer, 12% for wine, 40% for liquor, 16% for *sake* (Japanese rice wine) and 25% for *shochu* (Japanese spirits made from barley, sweet potato, or rice or any combination of these) [18].

2.3. Carotid ultrasound measures

Before the study began, sonographers at both centers received training for carotid scanning at the ultrasound laboratory in Pittsburgh. Carotid arteries were examined with an ultrasound scanner (Toshiba SSA-270A, Toshiba Medical Systems, Otawara, Japan) equipped with a 5-MHz linear array imaging probe [19]. With the participant in the supine position, arteries were viewed in transverse and longitudinal projections. The scans were recorded on videotape and sent to the laboratory for scoring. For the common carotid artery segment, both near and far walls were examined 2 cm proximal to the bifurcation (bulb). For the bulb area and internal carotid artery, measurements were taken of the far walls only (because near walls cannot be consistently visualized). Digitized images were used to trace the medial-adventitial and intima-lumen interfaces across 1-cm lengths and to compute the IMT for each segment. Average intima-media thickness (AveIMT) was calculated from the mean of both the right and left carotid arteries of the 3 segments (8 locations total). A trained investigator at the central laboratory at the University of Pittsburgh performed the ultrasound measurements. Under continuous quality-assessment programs, correlation coefficients between sonographers and between readers for average IMT were 0.96 and 0.99, respectively [19].

2.4. Statistical analysis

SAS version 9.1 for Windows (SAS Institute, Cary, NC) was used. Because the number of participants was not large, and there were 106 participants in the 2 to 3 times per week fish consumption category, and furthermore no participants were in the fewer than once per month and rare or never categories, they were classified into the 2 groups according

Table 1
Characteristics according to fish consumption in randomly selected 250 Japanese men aged 40 to 49 years in Shiga (2002-2004)

	Fish consumption		*P*
	<4 times/wk	≥4 times/wk	
n (total = 250)	147	103	
AveIMT (mm)	0.623 ± 0.068	0.605 ± 0.065	.03
Age (year)	45.2 ± 2.8	45.1 ± 2.8	.63
Height (cm)	171 ± 5	167 ± 6	.15
BMI (kg/m^2)	23.6 ± 3.0	23.9 ± 3.1	.56
Waist circumference (cm)	85.1 ± 8.2	85.7 ± 8.6	.60
SBP (mm Hg)	125 ± 16	125 ± 17	.89
DBP (mm Hg)	76 ± 12	77 ± 12	.63
Diabetes (%)	6.8	1.9	.08
Lipid medication (%)	4.1	1.9	.34
Smoking (%)	48.3	50.5	.73
Pack-years	20.2 ± 19.0	20.4 ± 15.9	.94
Drinker (%)	61.9	73.8	.0496
Alcohol (g/d)	22.4 ± 27.1	31.8 ± 29.2	.01
CRP (mg/L)	1.0 ± 2.5	0.5 ± 0.8	.03
Insulin (μU/mL)	10.8 ± 4.8	9.8 ± 4.1	.11
Glucose (mg/dL)	107 ± 19	105 ± 10	.38
HOMA-IR	2.9 ± 1.8	2.6 ± 1.1	.047
LDL-C (mg/dL)	137 ± 37	130 ± 33	.11
HDL-C (mg/dL)	53 ± 13	55 ± 12	.24
TG (mg/dL)	150 ± 73	159 ± 82	.38

Lipid medication indicates subjects are on lipid-lowering medication; pack-years, pack-years of smoking; drinker, drinking alcohol 2 or more days per week.

to fish consumption as fewer than 4 times per week and 4 or more times per week around the median of fish consumption categories. Because the distributions of serum TG and CRP were positively skewed, a logarithmic transformation was used to normalize the distribution. The χ^2 test was used to compare dichotomous variables, and Student t test was used to compare means between the 2 groups according to fish consumption.

Spearman partial correlation coefficients were calculated for AveIMT and fish consumption (in 8 categories assigned 1 to 8 from low to high fish consumption frequencies), smoking (pack-years of smoking), waist circumference, systolic (SBP) and diastolic blood pressure (DBP), alcohol consumption per day, LDL-C, HDL-C, log-transformed TGs, log-transformed CRP, and HOMA-IR after adjustment for age.

Analysis of covariance was used to examine the contribution of fish consumption to AveIMT by adjusting for age (model 1); model 1 + pack-years of smoking (model 2); model 2 + waist circumference, SBP, and alcohol consumption (model 3); model 3 + diabetes, on lipid-lowering medications (model 4); model 4 + LDL-C, HDL-C, and $\log_{10}$(TG) (model 5); and finally, model 5 + $\log_{10}$(CRP) (model 6).

All P values were 2-tailed and $P < .05$ was considered significant. Data are presented as the mean ± SD unless stated otherwise.

3. Results

The characteristics in each fish consumption group are shown in Table 1. There were 147 men in the fewer than 4 times per week fish consumption group and 103 men in the 4 or more times per week group. None of the participants showed any overt atherosclerosis by carotid ultrasonic examination. The mean AveIMT was significantly higher in the low fish consumption group than in the high fish consumption group. The mean alcohol consumption was larger in the high fish consumption group than in the low fish consumption group. The mean CRP and HOMA-IR were significantly lower in the high fish consumption group than in the low fish consumption group. No significant differences in the 2 groups were found in the other variables.

Spearman partial correlation coefficients for AveIMT, fish consumption, and the other variables are shown in Table 2. AveIMT was significantly inversely correlated with fish consumption, pack-years of smoking, and HDL-C, and positively correlated with waist circumference, SBP and DBP, LDL-C, log-transformed TGs, log-transformed CRP, and HOMA-IR. Fish consumption was significantly inversely correlated with AveIMT, waist circumference, log-transformed CRP, and HOMA-IR, and positively correlated with pack-years of smoking, diastolic blood pressure, alcohol consumption, LDL-C, and HDL-C.

The results of analysis of covariance for the AveIMT difference between the 2 groups are shown in Table 3. After adjustment for age, pack-years of smoking, waist circumference, and alcohol consumption, the difference remained statistically significant. After further adjustment for diabetes and whether or not on lipid-lowering medications, the difference still remained statistically significant (model 4, P = .044). With further adjustment including LDL-C, HDL-C, and log-transformed TG, the statistically significant difference in the AveIMT between the 2 groups started to disappear (model 5, P = .64). With final adjustment including log-transformed CRP, in addition, the statistically significant difference in the AveIMT between the 2 groups was reduced further (model 6, P = .104).

Table 2
Partial correlation analyses adjusted for age in randomly selected 250 Japanese men aged 40 to 49 years in Shiga (in 2002-2004)

	AveIMT		Fish consumption	
	β estimate	P	β estimate	P
AveIMT	1.000		−0.253	<.0001
Fish consumption (times per week)	−0.253	<.0001	1.000	
Pack-years	−0.130	.004	0.302	<.0001
Waist circumference	0.383	<.0001	−0.301	<.0001
SBP	0.141	.002	0.033	.468
DBP	0.085	.061	0.096	.035
Alcohol	−0.055	.227	0.287	<.0001
LDL	0.160	.0004	−0.015	.742
HDL	−0.173	.0001	0.197	<.0001
$\log_{10}$(TG)	0.094	.039	0.058	.203
$\log_{10}$(CRP)	0.250	<.0001	−0.378	<.0001
HOMA-IR	0.170	.0002	−0.181	<.0001

Pack-years indicates pack-years of smoking; drinker, drinking alcohol 2 or more days per week.

Table 3
Analysis of covariance for AveIMT difference according to fish consumption

Models	P
Model 1: age	.039
Model 2: model 1+ pack-years	.039
Model 3: model 2 + waist circumference, SBP, alcohol consumption	.031
Model 4: model 3 + diabetes, lipid medication	.044
Model 5: model 4 + LDL, HDL, $\log_{10}$(TG)	.064
Model 6: model 5 + $\log_{10}$(CRP)	.104

4. Discussion

The present study demonstrated that the AveIMT in those who ate fish more often was thinner than that in those who ate fish less often, although none of the participants showed any overt atherosclerosis on carotid ultrasonic examination. Adjustment for atherosclerotic risk factors but without blood chemical data did not eliminate the statistically significant difference in the AveIMT between the 2 groups. However, after further adjustment for blood chemical data in the model, the statistically significant difference disappeared. Hino et al [20], in their population-based study with 1920 subjects in Japan, showed that the intake of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid was inversely related to IMT. The mean age of their study subjects was around 63 years and that of the present study participants was 45 years. Therefore, the present study demonstrated that fish consumption was inversely related to atherosclerosis even in middle age.

Although we did not specify portion sizes on the food frequency questionnaire (and thus we do not have data on the amount of n-3 PUFA consumed by the participants), according to the INTERMAP study conducted between 1996 and 1998, the mean dietary intake values of n-3 PUFA, EPA, and DHA in this area for men aged between 40 and 49 years were 3.22, 0.38, and 0.66 g, respectively, and those for the male participants in the United States were 2.20, 0.06, and 0.12 g, respectively [21]. Hino et al [20] reported that these values for their participants were 2.22, 0.32, and 0.52 g, respectively. Thus, EPA and DHA intake values by the participants in the present study were comparable to those in the study by Hino et al.

The inverse association of fish consumption with CRP by Spearman partial correlation coefficient analysis in the present study is similar to that in previous reports [22-26]. n-3 PUFA are thought to act directly by replacing arachidonic acid as an eicosanoid substrate and inhibiting arachidonic acid metabolism, and are also thought to act indirectly by altering the expression of inflammatory genes through effects on transcription factor activation [22]. Long-chain n-3 PUFA also gives rise to a family of anti-inflammatory mediators termed resolvin [22]. However, metabolic studies on the effect of n-3 PUFA on inflammatory markers gave conflicting results. Some studies suggested that the intake of fish oils decreased inflammatory markers [23,24]; others found no effects [27-29]. A population-based study by Zampelas et al [25] found that fish consumption was independently inversely associated with CRP and other inflammatory markers. The present study may be the second population-based study to show that fish consumption was independently associated with CRP.

An inverse association of fish consumption with HDL-C in the present study is in line with findings of previous reports. Okuda et al [30] have shown that n-3 PUFA intake was positively associated with serum HDL-C in men. Inverse associations of fish consumption with HOMA-IR are consonant with previous reports that suggested n-3 PUFA might prevent insulin resistance [31-33]. Significant positive associations of fish consumption with alcohol consumption as well as with pack-years of smoking by Spearman partial correlation coefficients analysis in the present study implies that those who ate fish more frequently also smoked more and consumed a larger amount of alcohol. These confounding effects of fish consumption, smoking, and alcohol consumption may be the reason why we observed an apparent inverse association between smoking and AveIMT. Thus, in the multivariate analysis of covariance, pack-years of smoking did not make a significant contribution to the AveIMT difference according to the fish consumption categories.

The associations of AveIMT with the atherosclerotic risk factors such as blood pressure, CRP, LDL-C, and HDL-C (inverse association) in the present study are in line with those of previous studies [34-37].

That the significant difference in the AveIMT between the 2 groups further disappeared after final adjustment for log-transformed CRP may imply that the suppression of inflammation is one intervening mechanism of fish consumption against atherosclerosis. However, the inclusion of CRP in the final model might have resulted in over-adjustment, because a higher CRP level might rather be a reflection of atherosclerosis per se, but not be one of the intervening mechanisms. In fact, Wilson et al [38] found that an elevated CRP concentration provided no further prognostic information beyond the traditional office risk factor assessment to predict future major cardiovascular events in the Framingham Heart Study sample. Therefore, the fact that the difference in the AveIMT remained almost statistically significant without CRP in the model in the present study may imply that factors other than n-3 PUFA that were related to fish consumption resulted in limiting the development of early atherosclerosis.

The main strengths of the present study are the following: (1) population-based random samples, (2) the collection of high-quality carotid ultrasound data at the central laboratory, and (3) the narrow age range of our participants, 40 to 49 years, which allowed us to minimize the confounding effects generated from the age of the participants. The study is limited by (1) a small sample size, (2) its cross-sectional design, and (3) the fact that we did not specify portion sizes on the food frequency questionnaire, and thus we do not have reliable nutrient intake values and total energy intake.

4.1. Conclusions

Fish consumption is associated with a lower incidence of atherosclerosis in middle-aged men, probably via its beneficial effects on inflammation.

Acknowledgment

This research was supported by a grant-in-aid, (A):13307016, from the Japanese Ministry of Education, Culture, Sports, Science and Technology and the National Institutes of Health grant R01 HL68200.

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