Fish Consumption and the Risk of Alzheimer Disease

Is It Time to Make Dietary Recommendations?

In this issue of the ARCHIVES, Morris and colleagues[1] report data from a remarkable prospective study of Alzheimer disease (AD) in a biracial community in Chicago, Ill (815 people, aged 65-94 years). They found that subjects who ate fish once a week or more had a 60% lower risk for developing AD than those who consumed fish less frequently. The data were statistically adjusted to correct for the effects of age, sex, ethnicity, education, stroke, hypertension, heart disease, apolipoprotein E (apo E) genotype, total caloric intake, and consumption of other fats or vitamin E. Intake of long-chain n-3 polyunsaturated fatty acids (PUFAs) and docosahexaenoic acid (omega-3) was associated with a reduced risk of developing AD over the 4 years of the study. Intake of α-linolenic acid or eicosapentaenpoic acid was not associated with disease after adjustment. Intake of α-linolenic acid, found in vegetable oils and nuts, was protective only in people with the *apoE ϵ4* allele, and total n-3 fatty acid intake was protective only in women. These data and other work in the area[1,2] suggest that consumption of PUFAs found in fish, vegetable oils, and nuts may reduce AD risk.

See also page 940

The causal web for AD is remarkably complex, as cardiovascular disease, stroke, hypertension, and diabetes are all risk factors for the disease.[3] Consequently, dietary and other hazards enhancing the presence of these conditions increase the probability of getting AD as well. The strong influence of *apo E* genotype on the inherited risk of the disease is a powerful sign that lipid homoestasis is important, as the main function of apo E protein is lipid transport. High intake of saturated fat along with high total fat and cholesterol levels have been reported to increase the risk of the disease.[4] Morris and colleagues[2] have recently reported in the ARCHIVES that the intake of saturated or *trans*-unsaturated fats increases the risk of AD, while the intake of unsaturated, unhydrogenated fats is protective. Moreover, several studies have shown that the increased dietary intake of saturated fats enhances cerebral amyloid-β deposition in mouse, rabbit, and monkey models of AD.[3] A recent report, however, from the Rotterdam study did not demonstrate any influence of fat intake on dementia risk.[4] The dietary intake of polyunsaturated fats and fish has also been shown to decrease the risk of heart disease,[2] nonhemorrhagic stroke (≥2 servings per week),[5,6] as well as AD.[1,2] However, a population-based case-control study in Spain (with a high nonresponse rate near 60%) reported that high levels of fish consumption increased stroke risk.

The mechanisms by which fish intake may be protective against the development of AD are numerous. The PUFAs (including docosahexaenoic acid) found in fish are present in reduced levels in the plasma and brains of subjects with AD and have been reported to improve brain functioning in animals.[1,4] Animal studies provide ample evidence to support the beneficial effects of long-chain n-3 fatty acids on cardiovascular function, including anti-inflammatory, antiarrhthmic, antiaggregant, and antiatherogenic effects. The PUFAs are actually incorporated into atherosclerotic plaques, enhancing their stability.[7] Consumption of polyunsaturated fats in fish and vegetable oils may also lower serum cholesterol and triglyceride levels. Effects on high-density lipoprotein levels may also be important. Fish oil has been found to be protective in a monkey model of amyloid-β deposition. Consumption of PUFAs may alter membrane stability and thereby influence amyloid-β precursor protein cleavage by the amyloidogenic β-secretase. Moreover, it has been reported that rats fed PUFAs show a 10-fold increase in transthyretin expression.[8] Transthyretin is an amyloid-binding protein that may enhance amyloid-β protein clearance from the brain to blood.[8]

Fish is a good source of high-quality protein, as well as PUFAs, and is low in saturated fats. However, the beneficial effects of PUFAs from fish may be counterbalanced by toxins. Fish may contain dangerous levels of polychlorinated biphenyls and mercury from coal-fired power plants (especially methylmercury).[9,10] Organomercury compounds are highly reactive and promote free radical formation and atherosclerosis, with negative influences on cardiovascular and central nervous system health.[9,10] High mercury levels in some fish species may decrease the cardioprotective effects of fish intake.[9] Current National Academy of Sciences (USA) recommendations advise pregnant women (or women who may become pregnant) to avoid fish with the highest levels of methylmercury (large predatory fish such as king mackerel, tilefish, shark, or swordfish) (see http://www.cfsan.fda.gov/~frf/sea-mehg.html, from the Food and Drug Administration Center for Food Safety and Applied Nutrition). Tuna also may contain mercury, but it has lower levels than the larger fish just listed. Salmon, haddock, cod, pollock, and sole generally contain lower mercury levels than larger fish and levels are generally low in smaller fish. Local contamination of rivers and lakes is also important to consider. Fish raised in farms may be safe from contamination (eg, tilapia), but contaminated feed and pollution may also be a problem. Cold water fish (salmon, mackerel, tuna) generally have the highest omega-3 fatty acid concentrations

There is now considerable evidence to suggest that diet may influence AD risk. The confluence of human and ani-

mal studies suggest that dietary recommendations may be offered to decrease the chance of getting the disease. It is desirable for people to consume fish frequently and lower their intake of saturated fat in meat and dairy products. High levels of consumption of fruit and vegetables that contain antioxidants are also desirable. It is important for obesity to be avoided (lowering the risk of diabetes and hypertension) through dietary control and physical exercise. Healthy fats in fish, vegetable oils, vegetables, and nuts should be encouraged, and fats from meat and dairy products minimized. Low levels of alcohol consumption may be advisable. Fish oil may be taken in capsule form (not cod liver oil). Data about vitamin E supplements and AD risk do not currently support its use. Dietary intake is best considered from the point of view of diet patterns, rather than individual foods. A high antioxidant/low saturated fat diet pattern with a greater amount of fish, chicken, fruits, and vegetables and less red meat and dairy products is likely to lower the risk of AD, as well as that for heart disease and stroke. Furthermore, B vitamin supplements, containing vitamins B_{12} and B_6, and folic acid lower plasma total homocysteine levels, possibly decreasing the risk of stroke, heart disease, and perhaps AD.

These recommendations have not yet been evaluated with a double-blind, multisite clinical trial. However, this dietary advice is fully in accordance with recommendations for lowering the risk of cardiovascular disease and diabetes. Furthermore, fish consumption is believed to lower the risk of prostate, gastrointestinal tract, and other cancers. A low-fat diet is also helpful in avoiding obesity and reducing the risk of hypertension. In addition, these dietary guidelines are low risk and inexpensive.

Many questions about the influences of fish intake on brain disease remain. What are the influences of *apo E* genotype on the handling of PUFAs? The *apo E* genotype influences blood lipid responses to dietary interventions, and we have found that the *apo E* genotype influences fat intake in early life.[11] Reported influences of fish intake and PUFAs on depression also deserve further study. The suggested quantity of fish intake desired is also unclear. In the Health Professional Follow-up Study of 43 671 men[5] a protective effect of fish intake on stroke was found, but a dose effect was not observed. However, a protective dose effect of fish intake against stroke was detected in the Nurses' Health Study cohort study of 79 839 women,[6] with the greatest effect seen in those women who consumed fish 5 or more times a week. A recent report of PUFAs causing increased plasma homocysteine levels requires confirmation. Better understanding of the physiological effects of PUFAs on amyloid-β protein production and clearance may aid in the development of new AD therapies.

Attention was drawn to dietary influences on health decades ago by observation of the low risk for cardiovascular disease in the Japanese and also in the Inuit of Greenland, populations with high levels of consumption of fish. Hendrie and colleagues[12] have reported a low risk of AD in the Cree in northeastern Canada, another population with high fish intake. We have found a high prevalence of AD in an Arab population in Israel with a low rate of fish consumption.[13] Cross-cultural epidemiological studies may provide valuable insights into complex diseases, which can then be further dissected with animal studies. More cross-cultural studies of AD are needed. It is possible that the protective effects demonstrated by Morris et al[1,2] were reflective of the influences of early (preclinical) stages of AD on dietary intake. It is well known that the disease influences eating habits, and it is clear that the cerebral processes of AD progress slowly for many years before onset of dementia. This is an important problem in AD epidemiology and suggests the need for longer-term prospective studies. Demographic projections predict a remarkable increase in aged populations in the United States in the 21st century (≥ 65 years from 12.4% in 2000 to 19.6% in 2030). The National Institutes of Health and other funding agencies should be encouraged to strongly support long-term longitudinal studies of aging (≥10 years), beginning in midlife, to uncover the complex interactive patterns that control the development of the brain diseases associated with aging.

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