The Role of Omega-3 Fatty Acids for the Treatment and Prevention of Cardiovascular Disease

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Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome

Abstract:

• The n-3 long-chain polyunsaturated fatty acids (n-3 PUFA) such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) have been reported to improve obesity-associated metabolic disorders including chronic inflammation, insulin resistance and dyslipidemia. Growing evidence points to adipose tissue as a target in mediating the beneficial effects of these marine n-3 PUFAs in adipose deposition and function. Therefore, in this manuscript we focus in reviewing the current knowledge about effects of marine n-3 PUFAs on adipose tissue metabolism and secretory functions. This review includes n-3 PUFAs actions on adipose tissue metabolism and insulin resistance. The effects of n-3 PUFAs on adipose tissue glucose uptake and insulin signaling are also summarized. Moreover, the roles of peroxisome proliferator-activated receptor (PPARs) and AMPK activation in mediating n-3 PUFAs actions on adipose tissue function are discussed. Finally, the mechanisms underlying the ability of n-3 PUFAs to prevent and/or ameliorate adipose tissue inflammation are also revised, focusing on the role of n-3 PUFAs-derived specialized proresolving lipid mediators such as resolvins, protectins, and maresins.

Martinez Fernandez L et al. Prostaglandins and Other Lipid Mediators; Vol 121, 24-41, Sept 2015

US Physicians Health Study

Consumption of at least 1 fish meal per week reduced the risk of sudden cardiac death by 52% compared to those consuming fish once a month.


Omega-3 fatty acids and adipose tissue function in obesity and metabolic syndrome

CVD Risk Reduction: Mechanisms of Action

Lower triglycerides and remnant lipoproteins
Reduce inflammation
Lower blood pressure
Lower resting heart rate
Improve heart rate variability
Increase baroreceptor control
Reduce the risk of fatal arrhythmias
Improve insulin sensitivity
Mildly inhibit platelet function and decrease risk for thrombosis
Improve endothelial function
Reduce features of inflammatory atherosclerotic plaque

American Journal of Hypertension 2014

Low-Chain Omega-3 Fatty Acids Eicosapentaenoic Acid and Docosahexaenoic Acid and Blood Pressure: A Meta-Analysis of Randomized Controlled Trials

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JAMA. 2002;287

Nurses Health Study

• Dietary consumption of 85,000 female nurses free from CVD and cancer were followed for 16 years.
• Higher consumption of fish and omega-3 associated with lower risk of CHD and CHD death

from:


Multivariate adjusted relative hazard of sudden death across increasing levels of fish intake per week. The solid line represents the maximum partial likelihood estimate of the smooth relative hazard function, using a restricted cubic spline model with 4 knots. The dotted lines represent pointwise 95% confidence intervals for the relative hazard function.

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JAMA. 2002;287
Epidemiologic Studies:

In 25 studies involving a total of 280,000 participants, there was an inverse association between fish consumption and morbidity or mortality from coronary heart disease.


Clinical Trials

Secondary Prevention of Cardiovascular Disease

Epidemiologic Studies:

In 25 studies involving a total of 280,000 participants, there was an inverse association between fish consumption and morbidity or mortality from coronary heart disease.


GISSI Prevenzione Trial

- Randomized 11,323 post MI patients with 1 capsule of 850 mg EPA/DHA in a 1:1:1 ratio versus placebo.
- After one year, patients taking the fish oil had a 23% reduction in total mortality and a 30% reduction in CV mortality. In addition, there was a highly significant 45% reduction in sudden cardiac death (SCD) after only 4 months.


The Relationship Between Fish Consumption and Stroke Incidence

The NHANES I Epidemiology Follow-up Study

- Objective: To assess the level of fish consumption as a risk factor for stroke.
- Methods: Participants were members of the National Health and Nutrition Examination Survey I (NHANES I) Follow-up Study, a prospective cohort study of a national sample. The sample included the subjects who were alive and invited to return for follow-up at the time of the second phase of the survey (1983-1984) and who responded.
- Results: White women aged 65 to 74 years who consumed fish more than once a week had an age-adjusted relative risk of stroke of 0.65 (95% CI, 0.49-0.86) compared with women who never consumed fish. White men aged 45 to 74 years who consumed fish more than once a week had an age-adjusted relative risk of stroke of 0.72 (95% CI, 0.51-1.01) compared with men who never consumed fish.
- Conclusions: White women who consumed fish more than once a week had significantly lower stroke incidence than those who never consumed fish. A similar protective effect was seen in black women and men combined. Further studies are needed to confirm these findings in other populations and to evaluate the role of fish in the prevention of stroke.


Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis.

- Objective: To examine the relationship of fish and omega-3 polyunsaturated fatty acid intake with risk of specific stroke subtypes.
- Methods: The Japan EPA Lipid Intervention Study (JELIS) was a randomised open-label, blinded endpoint analysis of 10,619 hypercholesterolaemic patients with a history of coronary artery disease who were given EPA treatment. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and cardiac death in patients with diabetes mellitus. Randomisation was based on cholesterol levels and history of coronary artery disease.
- Results: Among patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (95% CI, 0.76-0.90; P = .007). Among stroke subtypes, a significantly reduced risk of thrombotic infarction was found among women who ate fish 2 or 3 times per week (relative risk, 0.79; 95% CI, 0.63-0.99; P = .042) versus women who ate fish less than once per month. In hypercholesterolaemic patients, EPA treatment reduced major coronary events in Japanese women, but not in Japanese men. EPA treatment was associated with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and cardiac death in patients with diabetes mellitus. Randomisation was based on cholesterol levels and history of coronary artery disease.
- Conclusions: EPA is a promising treatment for prevention of major coronary events, and especially non-fatal coronary events, in Japanese hypercholesterolaemic patients.


Omega-3 FA Intake

- AHA Recommendations for Omega-3 FA Intake
  - Patients without documented CHD: Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in linoleic acid (flaxseed, canola, and soybean oils; flaxseed, canola, and soybean oils).
  - Patients with documented CHD: Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.
  - Patients needing triglyceride lowering: 2–4 grams of EPA+DHA per day provided as capsules under a physician’s care.

DART

- Diet and Reinfarction Trial (DART), men with recent MI showed that omega-3 PUFAs either in dietary oily fish or fish oil capsules reduced 20 year all-cause mortality by 29% and mortality from CHD by 61%.


Intake of Fish and Omega-3 Fatty Acids and Risk of Stroke in Women

- Objective: To examine the relationship of fish and omega-3 polyunsaturated fatty acid intake with risk of specific stroke subtypes.
- Methods: The Japan EPA Lipid Intervention Study (JELIS) was a randomised open-label, blinded endpoint analysis of 10,619 hypercholesterolaemic patients with a history of coronary artery disease who were given EPA treatment. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and cardiac death in patients with diabetes mellitus. Randomisation was based on cholesterol levels and history of coronary artery disease.
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Omega-3

- Should we measure?

Iso H, MD, PhD; et al. JAMA. 2001;285(3):304-312.
Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.

**OBJECTIVE:**
Dietary intake of n-3 polyunsaturated fatty acids from seafood is associated with a reduced risk of primary cardiac arrest.

**METHODS:**
A total of 334 case patients with primary cardiac arrest, aged 25 to 74 years, attended by paramedics during 1988 to 1994 were recruited from Seattle and King County, Washington. Spouses of case patients and control subjects were interviewed to determine a wide range of potential confounders. Population-based case-control study.

**RESULTS:**
Blood cell membrane n-3 polyunsaturated fatty acid level of 5.5 g of n-3 fatty acids per month (the mean of the third quartile and the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.4 to 0.8), after adjustment for potential confounding factors. Compared with a red blood cell membrane fatty acid composition, a biomarker of dietary n-3 polyunsaturated fatty acid intake.

Blood Omega-3 and Trans Fatty Acids in Middle-Aged Acute Coronary Syndrome Patients

We tested the hypothesis that lower blood omega-3 (ω-3) fatty acids (FAs) and/or higher levels of ω-6 FA have been associated with decreased risk of sudden cardiac death. Lower levels of ω-6 FA and fat intake from ω-6 fatty acids and trans FA from ω-6 and ω-3 fatty acids were associated with lower CVD risk factors and reduced cardiovascular events. Blood EPA + DHA may serve as a new, modifiable risk factor for ACS.

Conclusions

- The vast majority of clinical trial evidence supports the use of omega-3 fatty acids to lower CVD risk factors and reduce cardiovascular events.
- Omega-3 blood levels vary widely due to differences in intake and genetics.
- Clinical studies have demonstrated the importance of measuring omega-3 blood levels and suggest that low omega-3 levels can serve as a modifiable CVD risk factor.

Role of FADS1 and FADS2 polymorphisms in polyunsaturated fatty acid metabolism

Tissue availability of polyunsaturated fatty acids (PUFAs) depends on dietary intake and metabolic turnover and has a major impact on human health. Strong associations between variants in the human genes fatty acid desaturase 1 (FADS1) and fatty acid desaturase 2 (FADS2), encoding delta-6 desaturase and delta-5 desaturase, and blood levels of PUFAs and long-chain PUFAs (LC-PUFAs) have been reported. These genetic variants significantly associate with higher levels of total fatty acids (the mean of the lowest quartile) and lower levels of the blood image-3 index, ω-6 and ω-3 fatty acids. Blood EPA + DHA may serve as a new, modifiable risk factor for ACS.