Review

Omega-3 fatty acids and non-communicable diseases

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Objective To review the relation between dietary omega-3 polyunsaturated fatty acids (ω-3 PUFA) and non-communicable diseases.

Method Data were collected from scientific journals and conference publications, MEDLINE (1979 – 2002) and current content which included 68 prospective, cross-sectional, case control and dietary-intervention studies. Scientific paper selections were based on the association between ω-3 PUFA and non-communicable diseases.

Results ω-3 PUFA has beneficial effects on increasing heart rate variability, decreasing the risk of stroke, reducing both systolic and diastolic blood pressure, insulin resistance and glucose metabolism. Long chain ω-3 PUFA has anti-cancer and anti-inflammatory activities. ω-3 PUFA has also been reported to have a beneficial effect on attention-deficit/hyperactivity disorder and schizophrenia, and may be effective in managing depression in adults.

Conclusions Results from epidemiological and dietary intervention studies have shown that ω-3 PUFA represent powerfully a class of bioactive compounds and that dietary intake of ω-3 PUFA plays a critical role in human health in relation to non-communicable diseases.

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SOURCES OF OMEGA-3 POLYUNSATURATED FATTY ACIDS

Alpha-linolenic acid (ALA; 18:3n-3) together with linoleic acid (LA; 18:2n-6) are two essential fatty acids for humans. LA is the most predominant polyunsaturated fatty acids (PUFA) in our diet, which is commonly found in vegetable seed oils. ALA is less abundant than LA; ALA is also present in some vegetable oils such as perilla, flaxseed, canola, soybean and walnut oils. ALA and LA are the parent fatty acids of ω-3 and ω-6 series PUFA, which can be converted *in vivo* to C20 and C22 long chain (LC) PUFA. Fish and fish oil are the main sources of LC ω-3 PUFA, such as docosahexaenoic acid (DHA, 22:6n-3), eicosapentaenoic acid (EPA, 20:5n-3) and docosapentaenoic acid (DPA, 22:5n-3). Other sources of LC ω-3 PUFA include lean meat and meat products, offal, egg yolk, milk and dairy products.[1]

BLOOD PRESSURE

The effect of fish-derived LC ω-3 PUFA on blood pressure (BP) has been evaluated in a meta-analysis of 31 placebo-controlled trials involving 1356 subjects. The results indicated that systolic BP fell by 3.4 mmHg and diastolic BP fell 2.0 mmHg following ingestion of fish oil (5.6 g/d) in a group of hypertensive studies.[2] Two human studies recently provided further evidence of the importance of LC ω-3 PUFA on BP. In a dietary intervention study, 69 overweight (BMI > 25 kg/m^2) medication-treated hypertensive subjects were randomized to either a daily fish meal (3.65 g/d of LC ω-3 PUFA approximately), a weight reduction regimen, the two regimens combined, or a control regimen for 16 weeks, and 63 subjects completed the study. Both systolic and diastolic BP, body weight and heart rate significantly decreased in the fish diet group compared with the controlled diet group, even after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well

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as dietary macronutrients.[3] The second study was an observational study in which the effects of fish-derived ω-3 PUFA on blood pressure, platelet fatty acid levels and heart rate variability were investigated in 43 subjects (male 24, female 19, aged 18 to 62 years) with type 1 diabetes mellitus, and 38 subjects (male 24, female 14, aged 37 to 77 years) with type 2 diabetes mellitus (Christensen et al, 2001).[4] Each patient completed a food frequency questionnaire and provided a blood sample. BP, heart rate variability, plasma and lipoprotein lipids and platelet fatty acid composition were measured. The study found that fish intake was significantly positively associated with platelet membrane DHA levels. According to the platelet DHA levels, patients were divided into three tertiles, the first tertile (n = 14) had the lowest DHA level, the third tertile (n = 15) had the highest DHA level and the second tertile was in between. Compared with the first tertile, the third tertile had a significantly lower diastolic BP and higher 24-hour heart rate variability (increased heart rate variability has a beneficial effect on dysrhythmia). Platelet DHA level was significantly positively associated with 24-hour heart rate variability in patients with type 1 diabetes mellitus; however this association was not significant in patients with type 2 diabetes mellitus. In a double blind, randomized, placebo-controlled human study, it was found that EPA and DHA differed in their effects on BP and heart rate.[5] In this study, 55 overweight (BMI 25 – 30 kg/m^2) subjects, aged 20 – 65 years, were randomized to 4 g/d of purified EPA, DHA, or placebo (olive oil) capsules for 6 weeks. Compared with the placebo group, DHA significantly reduced both systolic and diastolic BP (measured over 24 hours) by 5.8 and 3.3 mmHg, and the waking systolic and diastolic BP by 3.5 and 2.0 mmHg, respectively ($P < 0.05$). Relative to the placebo group, heart rate over a 24-hour period, when awake and when asleep were significantly reduced by 3.5 ± 0.8, 3.7 ± 1.2 and 2.8 ± 1.2 bpm, respectively. On the other hand, EPA showed no significant effect on BP and heart rate. A recent animal study found that ω-3 PUFA deficiency in the perinatal period resulted in an increase in BP in the later life of Sprague-Dawley rats.[6] Although the study was carried out on rats, it implicated that an adequate ω-3 PUFA intake in early years may prevent high BP in later life in human.

PLASMA/SERUM AND LIPOPROTEIN LIPIDS

LA has been claimed to be the only fatty acid to appreciably lower plasma/serum total and LDL-cholesterol when substituted for carbohydrates in diet; saturated fatty acids cholesterolemic and *cis* monounsaturated fatty acid were reported to be neutral in earier studies.[7,8] Recent dietary intervention studies found that ALA derived from plant sources had a similar effect on plasma/serum total and LDL-cholesterol, compared with LA.[9,10] ω-3 PUFA, especially those from marine oils reduce serum triacylglycerol (TAG) levels.[11,12] Serum TAG levels were significantly decreased compared with baseline in 66 healthy men (aged 36 ± 2 years) when they consumed ALA enriched diacylglycerol (ALA-DAG) for 4 weeks.[13] The mechanism of the hypotriacylglycerolemia of dietary DAG has been proposed to be due to the reduction of re-esterification (by glycerol and free fatty acid) and chylomicron assembly in the small intestine or to the reduction of subsequent secretion of chylomicron into the circulation.[14]

THROMBOSIS

Arterial thrombosis is generally recognised to play a major role in the transition from stable to acute ischaemic heart and cerebral diseases, manifested by unstable angina, acute thrombotic infarction and sudden death. Platelet aggregation is an early event in the development of thrombosis. It is initiated by thromboxane A_2 (TXA_2), a potent platelet aggregation agent and vascular contractor, produced from arachidonic acid (AA; 20:4n-6), a long chain ω-6 PUFA in the platelet membrane.[15,16] EPA is released from phospholipids of the platelet membrane and as a "false" substrate competes with AA for access to cyclooxygenase and produces an alternative form of thromboxane A_3 (TXA_3), which is relatively inactive in promoting platelet aggregation and vasoconstriction.[17] This situation can lead to a reduced TXA_2 production and thus a lower thrombosis tendency.[18,19] A diet with a high ω-6 to ω-3 PUFA ratio can cause a high tissue ω-6 to ω-3 PUFA ratio, i.e. increased AA to EPA ratio, which may promotes production of TXA_2, leads to increased thrombosis tendency.[20] Evidence from dietary intervention studies have found that the production of TXA_2 can be decreased by LC ω-3 PUFA in human[21,22] and animals,[23,24] and by plant ω-3 PUFA (ALA) in human[25] and animals.[26,27] Two current prospective cohort studies from USA Nurses' Health study, examined the effect of the intake of plants and fish-derived ω-3 PUFA on ischemic heart and cerebrovascular diseases in women. In the first study, the dietary intake of ALA was calculated from a food frequency questionnaire completed in 1984 by 76 283 nurses, aged 38 – 63 years, who did not have a previous history of cardiovascular disease and/or cancer. There were 597 cases of nonfatal myocardial infarction and 232 cases of fatal ischemic heart disease documented during 10 years of follow-up. After the adjustment of confounding factors, the result showed that a higher intake of ALA was significantly associated with reduced risk of fatal ischemic heart disease in this study population.[28] In the second study, 79 839 female nurses, aged 34 to 59 years in 1980, without prior diagnosed cardiovascular disease, cancer, and history of diabetes and hypercholesterolemia, completed a food frequency questionnaire. After 14 years of follow-up, 574 strokes were documented, of which 303 were ischemic strokes (264 thrombotic and 39 embolic infarctions). Compared with women who ate fish less than once per month, those with higher intake of LC ω-3 PUFA from fish had a lower risk of total stroke. Among stroke subtypes, a significantly reduced risk of thrombotic infarction was found among women who ate fish two or more times per week.[29] These data indicates that higher consumption of fish is associated with a reduced risk of thrombotic infarction. These results confirmed that an increased dietary ω-3 PUFA intake is protective against cardiovascular thrombotic infarction.

CANCERS

Numerous studies have investigated the effect of dietary individual fatty acids on cancers in experimental models, however, there are only a few publications on human studies. Consumption of fatty fish, high in LC ω-3 PUFA, showed a decreased risk of prostate cancer in a population-based prospective study from Sweden, involving 6272 men.[30] In this study, it was reported that men who ate moderate or high amounts of fish had a two- to three-fold lower frequency of prostate cancer compared with men who ate no fish. DHA manifested more effective inhibitory activity than EPA on transcription factor activator protein 1 (AP-1), which is implicated in the development of cancer in an experimental animal model.[31] A recent prospective cohort study from Finland reported the effect of dietary fat and cholesterol on colorectal cancer in 9959 men and women free of diagnosed cancer.[32] Baseline information was collected from the subjects between 1967 to 1972, and 109 cases of colorectal cancer were documented in late 1999. After adjustment for other confounding factors, it was found out that a high cholesterol intake was associated with colorectal cancer, while total fat, saturated fat, monounsaturated fat and PUFA were not significantly associated with colorectal cancer risk. Compared with ω-6 PUFA, LC ω-3 PUFA from fish oil had a protective effect on development of colon cancer in rats.[33] Conjugated linoleic acid (CLA), which is commonly a mixture of several isomers, the main ones being *cis*-9, *trans*-11-18:2 and *trans*-10, *cis*-12-18:2 (Ip et al, 1991),[34] have been shown to exhibit anticancinogenic properties in various animal models and cultured human tumor cells.[35-39] A recent study has compared the effect of CLA and conjugated linolenic acid on cultured human tumor cells, and the results have indicated that conjugated linolenic acid is more cytotoxic to human tumor cells than CLA.[40]

INFLAMMATION

AA is a substrate of pro-inflammatory eicosanoids such as prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4), while LC ω-3 PUFA DHA and EPA from fish oil, and ω-6 PUFA gamma-linolenic acid (GLA; 18:3n-6) are substrate for eicosanoids, which are antagonistic towards those produced from AA.[41] LC ω-3 PUFA and GLA are reported to have anti-inflammatory effects; in particular, LC ω-3 PUFA is thought to result in the amelioration of rheumatoid arthritis and related disorders.[42] AA derived leukotrienes (LTs), recognized as a "slow-reacting substance anaphylaxis", are mediators of allergic responses and inflammation.[43] AA can increase the formation of other pro-inflammatory substances, such as cytokines, TNFα, interleukin-6 and reactive oxygen species as reviewed by Darlington and Stone (2001).[44] LC ω-3 PUFA EPA and DHA compete with AA for cyclooxygenase and lipoxygenase, which results in a decreased production of AA-derived pro-inflammatory eicosanoids, cytokines, interleukin-6 and reactive oxygen species.[45] The 5-series of LTs can be produced from EPA, which are inactive relative to the AA-derived 4-series of LTs.[42,46] GLA can be elongated *in vivo* to 20:3n-6, which is an immediate precursor of prostaglandin E_1, an eicosanoid with known anti-inflammatory and immunoregulatory properties.[47,48] A recent study found that GLA reduces interleukin-1b (IL-1b, an important mediator of the joint tissue injury response and inflammation) production by human monocytes *in vitro*.[49]

NEUROPSYCHIATRIC DISORDERS

Manic-depressive illness (bipolar disorder), depression and schizophrenia are common neuropsychiatric disorders. Results from case-controlled clinical trails have shown that LC ω-3 PUFA can play a regulating role in neuropsychiatric performance. A low serum/plasma cholesterol concentration has been suggested to be associated with an increased risk of suicide and depression.[50] Results from a recent 4-month, double-blind, placebo-controlled trial involving 30 patients with type Ⅰ or Ⅱ bipolar disorder (aged 18 to 65 years), showed that episodes of severe mania and depression were significantly reduced in the LC ω-3 PUFA supplementation group (n = 14) (9.6 g/d), compared with the placebo group (n = 16).[51] Decreased LC ω-3 PUFA has been reported in serum phospholipid and cholesteryl ester samples of depressive patients,[52,53] and in erythrocyte membranes of schizophrenic patients.[54,55] As reviewed by Richardson and Puri (2000)[56] and Kidd (2000),[57] abnormalities of C20 and C22 PUFA, such as 20:4n-6, 20:5n-3 and 22:6n-3, are associated with attention-deficit/hyperactivity disorder. A recent prospective 5 – 8 years follow-up study, involving 29 133 men (aged 50 – 69 years), showed that low serum cholesterol concentrations were associated with low mood, which resulted in an increased risk of hospital treatment, due to the onset of major depression or suicide.[58]

A recent case-controlled study found that serum cholesterol concentration was significantly lower in parasuicide subjects, with mean age of 44 ± 21 years, compared with 331 sex- and age-matched controls ($P < 0.001$).[59] It has been reported that a low serum cholesterol level was strongly associated with violent behavior among 20 psychiatric patients.[60] These results suggest that the widespread use of cholesterol lowering drugs could lead to increased changes in mood. Mechanisms of ω-3 PUFA's effect on neuropsychiatric disorders may be through influencing the biophysical properties of the neuronal membrane.[50] Biophysical properties of synaptic membranes directly affect neurotransmitter biosynthesis, signal transduction, uptake of serotonin, binding of β-adrenergic and serotonergic receptors and monoamine oxidase activity. These factors are all implicated in neurobiology. It has been reported that 20:5n-3 is able to reverse the phospholipid abnormalities in schizophrenia via inhibition of PUFA-specific phospholipase A_2, an enzyme which removes PUFA from the sn-2 position of membrane phospholipids or by activation of a fatty acid CoA-ligase.[54] It is also possible that ω-3 PUFA operate through N-acylethanolamines (NAEs) and 2-acylglycerols, since these lipids are endogenous ligands for the cannabinoid receptors found predominantly in the brain.[61] In piglets, brain levels of NAEs increased 4-fold for 20:4n-6, 5-fold for 20:5n-3, 9-fold for 22:5n-3 and 10-fold for 22:6n-3 after being fed a diet containing 20:4n-6 and 22:6n-3 for 18 d, compared with piglets who were without 20:4n-6 and 22:6n-3.[62]

DIABETES MELLITUS AND OBESITY

Evidence from dietary intervention and prospective follow-up studies indicate that dietary intake of PUFA could be beneficial, whereas cholesterol, *trans* and saturated fatty acids could adversely affect insulin resistance and glucose metabolism. In a large ($n = 110\,660$) and long-term (6 years) intervention study from China, the Da Qing impaired glucose tolerance (IGT) and Diabetes study, the dietary treatment group and physical exercise group had a significantly lower cumulative diabetes incidence compared with the control group.[63] The 110 660 subjects (aged 25 to 74 years), were recruited from 33 health care clinics in 1986. After health examination screening tests, 577 subjects were classified as having impaired glucose tolerance. The subjects were randomized into a clinical trial group, either to a control group or to one of the three active intervention groups: diet only (low total fat, PUFA replacing saturated fat and high fiber), physical exercise only, and diet plus exercise. After 6 years, the cumulative diabetes incidence was significantly lower in the dietary treatment group (43.8%), the physical exercise group (41.1%) and the diet plus exercise group (46.0%), compared with the control group (67.7%) ($P < 0.05$). A more recent similar randomized intervention study from Finland, involving 522 overweight ($BMI = 31 \pm 4.6\ kg/m^2$) subjects (aged 55 ± 7 years), with impaired glucose tolerance, were divided into an intervention group ($n = 265$) and a control group ($n = 257$).[64] The subjects in the intervention group were given individual advice on dietary intake of energy, total and saturated fat, and moderate physical exercise. After 4 years, the intervention group had a significantly lower cumulative diabetes incidence than the control group (11% vs 23%, $P < 0.001$). Two recent, large prospective follow-up studies from USA showed that PUFA and vegetable fat have a protective effect on type 2 diabetes. The first study examined the relationship between dietary fat intake and risk of type 2 diabetes in 84 204 female nurses (aged 34 – 59 years) in 1980.[65] A total of 2507 cases of type 2 diabetes was documented during the 14 years of follow-up. The risk of type 2 diabetes was significantly positively associated with dietary intake of *trans* fatty acids and cholesterol, and negatively associated with vegetable fat, ω-3 and ω-6 PUFA. In the second study, the association between intake of dietary fat and incidence of type 2 diabetes was examined in 35 988 elder Iowa women (aged 55 – 69 years) in 1986, in which a total of 1890 cases of type 2 diabetes was reported.[66]

A recent study on 1,3-DAG, in which the amount of ALA was 61%, showed a reduction of body weight and visceral fat in mice fed with a high sucrose diet. In this study, the leptin and insulin levels increased in the high TAG group over a 20 weeks period, however replacement of 3% (weight %) of TAG by the ALA-DAG was associated with a reduction in insulin and leptin levels.[67] A study in human on calorie restricted diets using 2.5 to 3.7 g/d of ALA-DAG, containing 49% ALA, for 12 to 16 weeks showed a significant reduction in body fat.[13] A second study in human, using 2 g/d of ALA-DAG with 59% ALA, for 6 to 12 weeks, showed a significant reduction in visceral fat, a significant reduction in VLDL-TAG levels, and a significant increase in resting oxygen consumption. The authors concluded that the reduction in visceral fat was the result of reduced TAG synthesis and increased oxidation of fatty acids.[68]

CONCLUSION

Results from recent human and animal studies show that ω-3 PUFA are powerful bioactive compounds. ALA from plant sources had a similar effect on plasma/serum total and LDL-cholesterol, compared with LA. The marine LC ω-3 PUFA and ALA (present in DAG form) reduce serum TAG. ALA in DAG form has also been reported to have anti-obesity effects. Conjugated α-linolenic acid is more cytotoxic to human tumor cells compared with CLA. ω-3 PUFA have beneficial effects on increasing heart rate variability, decreasing risk of stroke, reduction of both systolic and diastolic blood pressure and may be effective in managing depression in adults. DHA has been reported to have a beneficial effect on hyperactive children. Decreased tissue levels of LC ω-3 PUFA are associated with neuropsychiatric disorders. These data show that ω-3 PUFA plays a critical role in human health in relation to cardiovascular disease, cancer, diabetes mellitus, and neuropsychiatric disorders.

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