Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis

OBJECTIVE: To determine the efficacy of fish oil derived (n-3) fatty acid supplementation (3-6 capsules/day) in subjects with rheumatoid arthritis (RA) whose (n-6) fatty acid intake in the background diet was < 10 g/day, compared to olive/corn oil capsule supplement over a 15 week period. METHODS: A placebo controlled, double blind, randomized 15 week study to determine the effect of supplementation on clinical variables in 50 subjects with RA whose background diet was naturally low in (n-6) fatty acids. Fish oil containing 60% (n-3) fatty acids was supplemented at a rate of 40 mg/kg body weight. RESULTS: Analysis of 9 clinical variables indicated there was a significant difference (p < 0.02) between control and treatment groups. Five subjects in the treatment group and 3 in the control group met the American College of Rheumatology 20% improvement criteria. Dietary supplementation resulted in a significant increase in eicosapentaenoic acid in plasma and monocyte lipids in the supplemented group. CONCLUSION: The findings suggest that fish oil supplementation that delivers (n-3) fatty acids at a dose of 40 mg/kg body weight/day, with dietary (n-6) fatty acid intake < 10 g/day in the background diet, results in substantial cellular incorporation of (n-3) fatty acids and improvements in clinical status in patients with RA. Volker D, Fitzgerald P, Major G, Garg M. J Rheumatol. 2000 Oct;27(10):2343-6.

The effects of dietary fatty acid supplementation on endothelial function and vascular tone in healthy subjects

OBJECTIVE: Evaluation of the effects of supplementation of n-3 and n-6 fatty acids on vascular tone and endothelial function in healthy men and women aged 40 to 65 years. METHODS: In a double-blind, randomised, placebo controlled study, 173 healthy volunteers took one of six oil supplements for 8 months. Supplements were placebo, oleic acid rich sunflower oil, evening primrose oil, soya bean oil, tuna fish oil, and tuna/evening primrose oil mix. Endothelium-dependent and independent vascular responses were measured in the forearm skin using laser Doppler imaging following iontophoretic applications of acetylcholine and sodium nitroprusside, respectively. RESULTS: Acetylcholine, but not sodium nitroprusside responses were significantly improved after tuna oil supplementation (P=0.02). Additionally, there were significant positive correlations between acetylcholine responses and n-3 fatty acid levels in the plasma and erythrocyte membrane phospholipids after tuna oil supplementation. No significant changes in vascular response were seen after supplementation with any of the other oils. CONCLUSIONS: Fish oil supplementation has a beneficial effect on endothelial function, even in normal healthy subjects. Modification of the diet by an increase of 6% in eicosapentaenoic acid and 27% in docosahexaenoic acid (equivalent to eating oily fish 2-3 times/week) might have significant beneficial effects on cardiovascular function and health. Khan F, Elherik K, Bolton-Smith C, Barr R, et al. Cardiovasc Res. 2003 Oct 1;59(4):955-62.

The effect of dietary omega-3 fatty acids on coronary atherosclerosis: A randomized, double-blind, placebo-controlled trial

BACKGROUND: Epidemiologic studies, studies of mechanisms of action, and many animal studies indicate that dietary intake of omega-3 fatty acids has antiatherosclerotic potential. Few trials in humans have examined this potential. OBJECTIVE: To determine the effect of dietary intake of omega-3 fatty acids on the course of coronary artery atherosclerosis in humans. DESIGN: Randomized, double-blind, placebo-controlled, clinically controlled trial. SETTING: University preventive cardiology unit. PATIENTS: 223 patients with angiographically proven
coronary artery disease. INTERVENTION: Fish oil concentrate (55% eicosapentaenoic and docosahexaenoic acids) or a placebo with a fatty acid composition resembling that of the average European diet, 6 g/d for 3 months and then 3 g/d for 21 months. MEASUREMENTS: The results of standardized coronary angiography, done before and after 2 years of treatment, were evaluated by an expert panel (primary end point) and by quantitative coronary angiography. Patients were followed for clinical and laboratory status. RESULTS: Pairs of angiograms (one taken at baseline and one taken at 2 years) were evaluated for 80 of 112 placebo recipients and 82 of 111 fish oil recipients. At the end of treatment, 48 coronary segments in the placebo group showed changes (36 showed mild progression, 5 showed moderate progression, and 7 showed mild regression) and 55 coronary segments in the fish oil group showed changes (35 showed mild progression, 4 showed moderate progression, 14 showed mild regression, and 2 showed moderate regression) (P = 0.041). Loss in minimal luminal diameter, as assessed by quantitative coronary angiography, was somewhat less in the fish oil group (P > 0.1). Fish oil recipients had fewer cardiovascular events (P = 0.10); other clinical variables did not differ between the study groups. Low-density lipoprotein cholesterol levels tended to be greater in the fish oil group. CONCLUSION: Dietary intake of omega-3 fatty acids modestly mitigates the course of coronary atherosclerosis in humans. von Schacky C, Angerer P, Kothny W, et al. Ann Intern Med. 1999 Apr 6;130(7):554-62.

Effects of eicosapentaenoic acid on blood pressure, cell membrane fatty acids, and intracellular sodium concentration in essential hypertension

This study was designed to clarify the effects of orally administered eicosapentaenoic acid (EPA) on blood pressure, intracellular sodium content, and cell membrane fatty acid composition in patients with essential hypertension. After a 4-week run-in period, a study group of 17 male patients was assigned to an 8-week treatment with EPA (2.7 g/day) or placebo in a randomized, double-blind fashion with a crossover at week 4. Systolic blood pressure (SBP) was lower after treatment with EPA than after treatment with placebo (152.9+/−17.3 vs. 162.6+/−20.6 mmHg; p<0.01), while diastolic blood pressure was not statistically different. Compared with the placebo treatment, EPA supplementation resulted in a decrease in intraerythrocyte sodium content (R-Na; 11.17+/−0.63 vs. 10.44+/−1.28 nmol/l cells; p<0.05) accompanied by an increase (p<0.001) in erythrocyte membrane EPA content. The increase in membrane EPA content was related to the decrease in SBP (r=−0.52, p<0.05) and the decrease in R-Na (r=−0.57, p<0.02) during EPA treatment. The decrease in R-Na correlated positively with the decrease in SBP (r=0.54, p<0.05), and correlated negatively with the change in Na+/K+ ATPase activity (r=−0.59, p<0.02). However, the change in Na+/K+ ATPase activity did not directly correlate with the change in membrane EPA content. In conclusion, oral EPA supplementation increased membrane EPA content and reduced SBP in patients with essential hypertension. Based on the association between the increase in membrane EPA content and the decrease in intracellular sodium concentration, EPA may lower blood pressure by altering the activities of the membrane sodium transport systems. Miyajima T, Tsujino T, Saito K, Yokoyama M. Hypertens Res. 2001 Sep;24(5):537-42.

Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial

Patients with depression have been extensively reported to be associated with the abnormality of omega-3 polyunsaturated fatty acids (PUFAs), including significantly low eicosapentaenoic acid and docosahexaenoic acid in cell tissue contents (red blood cell membrane, plasma, etc.) and dietary intake. However, more evidence is needed to support its relation. In this study, we conducted an 8-week, double-blind, placebo-controlled trial, comparing omega-3 PUFA (6.6 g/day) [corrected] with placebo, on the top of the usual treatment, in 28 patients with major depressive disorder. Patients in the omega-3 PUFA group had a significantly decreased score on the 21-item Hamilton Rating Scale for Depression than those in the placebo group (P < 0.001). From the preliminary findings in this study, omega-3 PUFA could improve the short-term course of illness and were well tolerated in patients with major depressive disorder. Su KP, Huang SY, Chiu CC, Shen WW. Eur Neuropsychopharmacol. 2003 Aug;13(4):267-71.
Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial

BACKGROUND: There is growing interest in the potential role of anti-inflammatory n-3 polyunsaturated fatty acids (n-3 PUFAs) in the prevention of allergic disease. OBJECTIVE: We sought to determine whether maternal dietary supplementation with n-3 PUFAs during pregnancy could modify immune responses in infants. METHODS: In a randomized, controlled trial 98 atopic, pregnant women received fish oil (3.7 g n-3 PUFAs per day) or placebo from 20 weeks' gestation until delivery. Neonatal PUFA levels and immunologic response to allergens were measured at birth. RESULTS: Eighty-three women completed the study. Fish oil supplementation (n = 40) achieved significantly higher proportions of n-3 PUFAs in neonatal erythrocyte membranes (mean +/- SD, 17.75% +/- 1.85% as a percentage of total fatty acids) compared with the control group (n = 43, 13.69% +/- 1.22%, P <.001). All neonatal cytokine (IL-5, IL-13, IL-10, and IFN-gamma) responses (to all allergens) tended to be lower in the fish oil group (statistically significant only for IL-10 in response to cat). Although this study was not designed to examine clinical effects, we noted that infants in the fish oil group were 3 times less likely to have a positive skin prick test to egg at 1 year of age (odds ratio, 0.34; 95% confidence interval, 0.11 to 1.02; P =.055). Although there was no difference in the frequency of atopic dermatitis at 1 year of age, infants in the fish oil group also had significantly less severe disease (odds ratio, 0.09; 95% confidence interval, 0.01 to 0.94; P =.045). CONCLUSIONS: These data suggest a potential reduction in subsequent infant allergy after maternal PUFA supplementation. More detailed follow-up studies are required in larger cohorts to establish the robustness of these findings and to ascertain their significance in relation to longer-term modification of allergic disease in children. Dunstan JA, Mori TA, Barden A, et al. J Allergy Clin Immunol. 2003 Dec;112(6):1178-84.

Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma

Omega-3 polyunsaturated fatty acids have anti-inflammatory effects in vitro, and high dietary levels are associated with a lower incidence of inflammatory diseases. However, only limited effects have been demonstrated in asthma. The effects of dietary supplementation with fish oil for 10 months in 29 children with bronchial asthma was investigated in a randomized controlled fashion. In order to minimize the effects of environmental inhaled allergens and diet, this study was performed in a long-term treatment hospital. Subjects received fish oil capsules containing 84 mg eicosapentaenoic acid (EPA) and 36 mg docosahexaenoic acid (DHA) or control capsules containing 300 mg olive oil. The daily dosages of EPA and DHA were 17.0-26.8 and 7.3-11.5 mg x kg body weight(-1), respectively. Asthma symptom scores decreased and responsiveness to acetylcholine decreased in the fish oil group but not in the control group. In addition, plasma EPA levels increased significantly only in the fish oil group (p<0.0088). No significant side-effects were observed. The present results suggest that dietary supplementation with fish oil rich in the omega-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid is beneficial for children with bronchial asthma in a strictly controlled environment in terms of inhalant allergens and diet. Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K. Eur Respir J. 2000 Nov;16(5):861-5.

Maternal DHA and the development of attention in infancy and toddlerhood

Infants were followed longitudinally to document the relationship between docosahexaenoic acid (DHA) levels and the development of attention. Erythrocyte (red-blood cell; RBC) phospholipid DHA (percentage of total fatty acids) was measured from infants and mothers at delivery. Infants were assessed in infant-control habituation at 4, 6, and 8 months augmented with psychophysiological measures, and on free-play attention and distractibility paradigms at 12 and 18 months. Infants whose mothers had high DHA at birth showed an accelerated decline in looking over the 1st year and increases in examining during single-object exploration and less distractibility in the 2nd year. These findings are consistent with evidence suggesting a link between DHA and cognitive development in infancy. Colombo J, Kannass KN, Shaddy DJ, et al. Child Dev. 2004 Jul-Aug;75(4):1254-67.
Essential fatty acids in visual and brain development

Essential fatty acids are structural components of all tissues and are indispensable for cell membrane synthesis; the brain, retina and other neural tissues are particularly rich in long-chain polyunsaturated fatty acids (LC-PUFA). These fatty acids serve as specific precursors for eicosanoids, which regulate numerous cell and organ functions. Recent human studies support the essential nature of n-3 fatty acids in addition to the well-established role of n-6 essential fatty acids in humans, particularly in early life. The main findings are that light sensitivity of retinal rod photoreceptors is significantly reduced in newborns with n-3 fatty acid deficiency, and that docosahexaenoic acid (DHA) significantly enhances visual acuity maturation and cognitive functions. DHA is a conditionally essential nutrient for adequate neurodevelopment in humans. Comprehensive clinical studies have shown that dietary supplementation with marine oil or single-cell oil sources of LC-PUFA results in increased blood levels of DHA and arachidonic acid, as well as an associated improvement in visual function in formula-fed infants matching that of human breast-fed infants. The effect is mediated not only by the known effects on membrane biophysical properties, neurotransmitter content, and the corresponding electrophysiological correlates but also by a modulating gene expression of the developing retina and brain. Intracellular fatty acids or their metabolites regulate transcriptional activation of gene expression during adipocyte differentiation and retinal and nervous system development. Regulation of gene expression by LC-PUFA occurs at the transcriptional level and may be mediated by nuclear transcription factors activated by fatty acids. These nuclear receptors are part of the family of steroid hormone receptors. DHA also has significant effects on photoreceptor membranes and neurotransmitters involved in the signal transduction process; rhodopsin activation, rod and cone development, neuronal dendritic connectivity, and functional maturation of the central nervous system. Uauy R, Hoffman DR, Peirano P, Birch DG, Birch EE. *Lipids*. 2001 Sep;36(9):885-95.

Eicosapentaenoic acid and docosahexaenoic acid reduce UVB- and TNF-alpha-induced IL-8 secretion in keratinocytes and UVB-induced IL-8 in fibroblasts

Omega-3 polyunsaturated fatty acids (n-3 PUFA) inhibit ultraviolet B (UVB)-induced inflammation and other inflammatory states, in vivo. We examined whether this may be mediated by modulation of interleukin (IL)-8, a chemokine pivotal to skin inflammation induced by UVB, in epidermal and dermal cells. We also explored the ability of n-3 PUFA to protect against tumor necrosis factor (TNF)-alpha induction of IL-8, and assessed relative potencies of the principal dietary n-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Pre-supplementation, both HaCaT keratinocyte and CCD922SK fibroblast cell lines showed dose-responses for UVB-induced IL-8 release (p<0.001), assessed 48 h post-irradiation. Cells were supplemented with > or =90% purified EPA, DHA, oleic acid (OA) or vehicle control, for 4.5 d. EPA and DHA supplements were bioavailable to keratinocytes and fibroblasts. In keratinocytes, EPA and DHA were shown to reduce basal secretion of IL-8 by 66% and 63%, respectively (p<0.05), and UVB-induced levels by 66% and 65% at 48 h after 100 mJ per cm², respectively, (p<0.01). A similar pattern occurred in fibroblasts, whereas OA had no influence on IL-8 release in either cell line. In addition, TNF-alpha-induced IL-8 secretion by keratinocytes was reduced by 54% and 42%, respectively, by EPA and DHA (p<0.001). Hence both n-3 PUFA inhibit production of UVB- and TNF-alpha-induced IL-8 in skin cells; this may be important in the photoprotective and other anti-inflammatory effects conferred by these agents. Storey A, McArdle F, Friedmann PS, Jackson MJ, Rhodes LE. *J Invest Dermatol*. 2005 Jan;124(1):248-55.

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