

Fish Oil and Lipids

Arch Intern Med. 2005 Apr 11;165(7):725-30.

Effect of different antilipidemic agents and diets on mortality: a systematic review.

Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC.

BACKGROUND: Guidelines for the prevention and treatment of hyperlipidemia are often based on trials using combined clinical end points. Mortality data are the most reliable data to assess efficacy of interventions. We aimed to assess efficacy and safety of different lipid-lowering interventions based on mortality data. **METHODS:** We conducted a systematic search of randomized controlled trials published up to June 2003, comparing any lipid-lowering intervention with placebo or usual diet with respect to mortality. Outcome measures were mortality from all, cardiac, and noncardiovascular causes. **RESULTS:** A total of 97 studies met eligibility criteria, with 137,140 individuals in intervention and 138,976 individuals in control groups. Compared with control groups, risk ratios for overall mortality were 0.87 for statins (95% confidence interval [CI], 0.81-0.94), 1.00 for fibrates (95% CI, 0.91-1.11), 0.84 for resins (95% CI, 0.66-1.08), 0.96 for niacin (95% CI, 0.86-1.08), 0.77 for n-3 fatty acids (95% CI, 0.63-0.94), and 0.97 for diet (95% CI, 0.91-1.04). Compared with control groups, risk ratios for cardiac mortality indicated benefit from statins (0.78; 95% CI, 0.72-0.84), resins (0.70; 95% CI, 0.50-0.99) and n-3 fatty acids (0.68; 95% CI, 0.52-0.90). Risk ratios for noncardiovascular mortality of any intervention indicated no association when compared with control groups, with the exception of fibrates (risk ratio, 1.13; 95% CI, 1.01-1.27). **CONCLUSIONS:** Statins and n-3 fatty acids are the most favorable lipid-lowering interventions with reduced risks of overall and cardiac mortality. Any potential reduction in cardiac mortality from fibrates is offset by an increased risk of death from noncardiovascular causes.

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Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J.

Greater fish oil consumption has been associated with reduced CVD risk, although the mechanisms are unclear. Plant-source oil omega-3 fatty acids (ALA) have also been studied regarding their cardiovascular effect. We conducted a systematic review of randomized controlled trials that evaluated the effect of consumption of fish oil and ALA on commonly measured serum CVD risk factors, performing meta-analyses when appropriate. Combining 21 trials evaluating lipid outcomes, fish oil consumption resulted in a summary net change in triglycerides of -27 (95% CI -33, -20)mg/dL, in HDL cholesterol of +1.6 (95% CI +0.8, +2.3)mg/dL, and in LDL cholesterol of +6 (95% CI +3, +8)mg/dL. There was no effect of fish oil on total cholesterol. Across studies, higher fish oil dose and higher baseline levels were associated with greater reductions in serum triglycerides. Overall, the 27 fish oil trials evaluating Hgb A(1c) or FBS found small non-significant net increases compared to control oils. Five studies of ALA were inconsistent in their effects on lipids, Hgb A(1c) or FBS. Four studies investigating the effects of omega-3 fatty acids on hs-CRP were also inconsistent and non-significant. The evidence supports a dose-dependent beneficial effect of fish oil on serum triglycerides, particularly among people with more elevated levels. Fish oil consumption also modestly improves HDL cholesterol, increases LDL cholesterol levels, but does not appear to adversely affect glucose homeostasis. The evidence regarding the effects of omega-3 fatty acids on hs-CRP is inconclusive, as are data on ALA

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Lipid-lowering drugs and essential omega-6 and omega-3 fatty acids in patients with coronary heart disease.

de Lorgeril M, Salen P, Guiraud A, Zeghichi S, Boucher F, de Leiris J.

BACKGROUND AND AIM: There are only little data about the effects of lipid-lowering drugs (LLDs) on the metabolism of essential n-6 and n-3 fatty acids in patients with established coronary heart disease (CHD). **METHODS AND RESULTS:** Male patients with CHD and high cholesterol levels (>6.2 mmol/L) were randomized (double-blind protocol) to receive either simvastatin 20mg (S) or fenofibrate 200mg daily (F) for 3 months. Dietary habits and plasma fatty acids were not different in the two groups at baseline. After treatment, there were significant changes in both the groups for the main n-6 fatty acids, with

an increase in arachidonate (from 6.5±1.7% of total fatty acids to 7.5±2.1, $p<0.001$ in S and from 6.2±1.4 to 6.8±1.4, $p<0.005$ in F) and a decrease in linoleate (from 26.9±3.9 to 24.2±3.6, $p<0.001$, and from 27.8±3.4 to 26.1±4.2, $p<0.05$, in S and F, respectively). In addition, there was a decrease in two major n-3 fatty acids (alpha-linolenate and docosahexanoate, both $p<0.05$), but only in F. **CONCLUSIONS:** For the first time in a double-blind randomized study in CHD patients, we report that LLDs significantly alter the metabolism of essential fatty acids that are critically important for the pathogenesis and prevention of CHD. Further studies are urgently needed to examine the effects of higher dosages of statins (as currently proposed to reduce more cholesterol) on these essential fatty acids in the clinical setting and the crucial questions of whether specific dietary intervention (combining low intake of n-6 fatty acids and high intake of n-3 fatty acids) may improve the effectiveness of these drugs.

J Med Assoc Thai. 2005 Feb;88(2):181-6.

Long-term treatment of N-3 PUFAS on plasma lipoprotein levels and fatty acid composition of total serum and erythrocyte lipids in hypertriglyceridemic patients.

Putadechakum S, Tanphaichitr V, Leelahagul P, Pakpeankitvatana V, Surapisitchart T, Komindr S.

The low incidence of coronary heart disease in Greenland Eskimos and Japanese fishermen who have high consumption of fish and seafood has called the attention in the role of eicosapentaenoic (EPA = 20:5n-3) and docosahexaenoic (DHA = 22:6n-3) acids, the major n-3 polyunsaturated fatty acids (PUFAs) in fish oils, in reducing cardiovascular risk. N-3 PUFAs may reduce serum lipids by promoting fatty acid oxidation and decrease VLDL producing from the liver, depress tissue arachidonate synthesis and alter the composition and tissue PUFAs. Plasma lipoprotein and fatty acid composition of total serum and erythrocyte lipids in 9 hypertriglyceridemic patients consisting of 4 males and 5 females aged 39-72 yr who attended the Nutrition Clinic, Ramathibodi Hospital were investigated. The study period consisted of 4 wks of dietary advice only followed by 48 wks of dietary advice with a daily intake of 6 g of fish oil capsules (FOC). Six grams of FOC provided 1080 mg of 20:5n-3 and 720 mg of 22:6n-3. Their plasma triglyceride (TG) levels at wk 0, 12, 24, 36, 48 were 356.7, 230.1, 209.7, 192.9, 227.4 mg/dL and M-particle (equivalent to very low density lipoprotein, VLDL) were 484.4, 354.8, 383.1, 349.7, 453.2 mg/dL respectively that decreased significantly, whereas their plasma low density lipoprotein cholesterol (LDL-C) levels at the same periods were 139.4, 164.9, 171.0, 157.1, 158.3 mg/dL that increased significantly. Serum and erythrocyte 20:5n-3 and 22:6n-3 in these subjects were significantly higher than those at wk 0 throughout the study. These findings indicate the bioavailability of 20:5n-3 and 22:6n-3 in TG lowering effect of FOC. Fatty acids from fish oil have a remarkable effect on the synthesis and clearance of TG-rich lipoproteins, especially VLDL and chylomicrons. Though daily treatment with 6 g of FOC has a striking effect in increasing plasma LDL-C levels.

Br J Nutr. 2004 Sep;92(3):477-83.

Circulating triacylglycerol and apoE levels in response to EPA and docosahexaenoic acid supplementation in adult human subjects.

Buckley R, Shewring B, Turner R, Yaqoob P, Minihane AM.

High doses of n-3 PUFA found in fish oils can reduce the circulating concentration of triacylglycerol (TG), which may contribute to the positive impact of these fatty acids on the risk of CVD. The present study aimed to establish the differential impact of EPA and docosahexaenoic (DHA) on plasma lipids and apo in adults. Forty-two normolipidaemic adult subjects completed a double-blind placebo controlled parallel study, receiving an EPA-rich oil (4.8 g EPA/d), DHA-rich oil (4.9 g DHA/d) or olive oil as control, for a period of 4 weeks. No effects of treatment on total cholesterol, LDL-cholesterol or HDL-cholesterol were evident. There was a significant 22 % reduction in TG level relative to the control value following the DHA treatment ($P=0.032$), with the 15 % decrease in the EPA group failing to reach significance ($P=0.258$). There were no significant inter-group differences in response to treatment for plasma apoA1, -C3 or -E levels, although a significant 15 % within-group increase in apoE was evident in the EPA ($P=0.006$) and DHA ($P=0.003$) groups. In addition, a within-group decrease in the apoA1:HDL-cholesterol ratio was observed in the DHA group, suggesting a positive impact of DHA on HDL particle size. The DHA intervention resulted in a significant increase in the proportion of EPA $P=0.000$ and DHA $P=0.000$ in plasma phospholipids, whilst significant increases in EPA $P=0.000$ and docosapentaenoic acid $P=0.002$, but not DHA $P=0.193$, were evident following EPA supplementation ($P<0.05$). Our present results indicate that DHA may be more efficacious than EPA in improving the plasma lipid profile.

J Am Acad Nurse Pract. 2004 Sep;16(9):384-95.

Treatment of hypertriglyceridemia with omega-3 fatty acids: a systematic review.

Lewis A, Lookinland S, Beckstrand RL, Tiedeman ME.

PURPOSE: To (a) critically appraise available randomized controlled trials (RCTs) addressing the efficacy of long-chain omega-3 fatty acids as secondary agents for prevention of hypertriglyceridemia and (b) make recommendations for clinical practice. **DATA SOURCES:** Two independent reviewers examined all RCTs from 1994 to 2003 identified in several databases, extracted data from each study, and used the previously tested Boyack and Lookinland Methodological Quality Index (MQI) to determine study quality. **CONCLUSIONS:** Ten studies reported long-chain omega-3 fatty acids to be effective in the treatment of hypertriglyceridemia. The average decrease in triglycerides was 29%, total cholesterol 11.6%, very low density lipoprotein (VLDL) 30.2%, and low-density lipoprotein (LDL) 32.5%. One study found LDLs to increase by 25%. The average increase in high-density lipoprotein was 10%. The overall average MQI score was 36% (range = 26% to 54%). Many of the RCTs had serious shortcomings, including short duration, lack of a power analysis, no intention-to-treat analysis, no report of blind assessment of outcome, and lack of dietary control as a confounding variable. **IMPLICATIONS FOR PRACTICE:** Overall study methodology was weak. Although the evidence supporting use of long-chain omega-3 fatty acids in the secondary prevention of hypertriglyceridemia is reasonably strong, until there are larger RCTs of better methodological quality, it is not recommended that practitioners treat hypertriglyceridemia with omega-3 fatty acid supplementation in lieu of lipid-lowering medications.

Am J Clin Nutr. 2004 Jul;80(1):45-50.

Triacylglycerol-rich lipoprotein margination: a potential surrogate for whole-body lipoprotein lipase activity and effects of eicosapentaenoic and docosahexaenoic acids.

Park Y, Jones PG, Harris WS.

BACKGROUND: Margination occurs when blood borne particles attach to the vessel wall. Triacylglycerol-rich lipoprotein (TRL) particles marginate when they bind to endothelial lipoprotein lipase (LpL). **OBJECTIVE:** This study was undertaken to determine whether TRL margination reflects in vivo LpL activity and whether n-3 fatty acids affect fasting and fed TRL margination. **DESIGN:** Healthy subjects (n = 33) began with a 4-wk, placebo (olive oil; 4 g/d) run-in period and were then randomly assigned to 4 wk of treatment with 4 g/d of ethyl esters of either safflower oil (SAF; control), eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA). Margination volume (MV) was calculated by subtracting true from apparent plasma volume. **RESULTS:** MVs were 3 times as great during the fasting state as during the fed state (P < 0.0001). In both the fasting and the fed states, MV was significantly correlated with plasma triacylglycerol and TRL half-lives. In the fed state, MV was also correlated with preheparin LpL, whereas in the fasting state it was not. There was no significant correlation between preheparin LpL and postheparin LpL in the fasting state. Relative to SAF, EPA and DHA supplementation resulted in higher MVs by 64% and 53% (both P < 0.001), respectively, in the fasting state, without significantly reducing fasting triacylglycerol concentrations. In the fed state, DHA doubled the MV (P < 0.05), whereas EPA had no significant effect. **CONCLUSIONS:** The correlations between MV and TRL half-lives and preheparin LpL suggest that MV could be a reflection of whole-body LpL binding capacity. The increases in MVs with EPA and DHA supplementation suggest that these fatty acids may increase the amount of endothelial-bound LpL or its affinity for TRL.

Am J Kidney Dis. 2004 Jul;44(1):77-83.

The effect of n-3 fatty acids on plasma lipids and lipoproteins and blood pressure in patients with CRF.

Svensson M, Christensen JH, Solling J, Schmidt EB.

BACKGROUND: Patients with chronic renal failure (CRF) have a high incidence of cardiovascular disease and increased premature mortality. n-3 Polyunsaturated fatty acids (PUFAs) are known to decrease plasma triglyceride levels, reduce blood pressure (BP), and have a cardioprotective effect in subjects with normal renal function. The aim of this study is to examine the effect of n-3 PUFAs on plasma lipid and lipoprotein levels and 24-hour ambulatory BP in patients with CRF. **METHODS:** Sixty-four patients with CRF, defined as a plasma creatinine level between 1.70 and 4.52 mg/dL (150 and 400 micromol/L), were included and randomly assigned to treatment with 2.4 g of n-3 PUFAs or control treatment (olive oil) for 8 weeks. Patients were evaluated by measurement of fasting plasma lipid and lipoprotein levels and 24-hour ambulatory BP recordings before and after the supplements. n-3 PUFA content was determined in cell membranes of granulocytes and adipose tissue samples to evaluate n-3 PUFA intake. **RESULTS:** There was a significant 8% increase in high-density lipoprotein cholesterol levels (P < 0.01) and a significant 21% decrease in serum triglyceride levels (P < 0.02) in the group administered n-3 PUFA supplements. There were no changes in total cholesterol or low-density lipoprotein cholesterol levels in any group, and n-3 PUFAs had no effect on 24-hour ambulatory BP. **CONCLUSION:** Supplementation with n-3 PUFAs had a favorable effect on lipoprotein profile in patients with CRF, whereas no effect on 24-hour ambulatory BP was observed.

Chin Med Sci J. 2004 Jun;19(2):145-9.

Effects of simvastatin combined with omega-3 fatty acids on high sensitive C-reactive protein, lipidemia, and fibrinolysis in patients with mixed dyslipidemia.

Hong H, Xu ZM, Pang BS, Cui L, Wei Y, Guo WJ, Mao YL, Yang XC.

OBJECTIVE: To evaluate the effects of simvastatin combined with omega-3 fatty acids on high sensitive C-reactive protein (HsCRP), lipidemia, and fibrinolysis in coronary heart disease (CHD) and CHD risk equivalent patients with mixed dyslipidemia. **METHODS:** A randomized, double-blind placebo controlled and parallel group trial was conducted. Patients with CHD and CHD risk equivalents with mixed dyslipidemia were treated with 10 or 20 mg simvastatin for 6-12 weeks. Following with the treatment of patients whose low-density lipoprotein cholesterol (LDL-ch) reaching goal level (< 100 mg/dL) or close to the goal (< 130 mg/dL), while triglyceride (TG) $> \text{or} = 200$ mg/dL and < 500 mg/dL, was combined with omega-3 fatty acids (3 g/d) or a placebo for 2 months. The effects of the treatment on HsCRP, total cholesterol (TC), LDL-ch, high-density lipoprotein cholesterol (HDL-ch), TG, lipoprotein (a) [LP (a)], apolipoprotein A1 (apoA1), apolipoprotein B (apoB), plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA) were investigated. Forty patients finished the study with each group consisting of twenty patients. **RESULTS:** (1) There were significant reductions of HsCRP, TG, TC, and TC/HDL-ch, which decreased by 2.16 ± 2.77 mg/L (38.5%), 94.0 ± 65.4 mg/dL (31.1%), 13.3 ± 22.3 mg/dL (6.3%), 0.78 ± 1.60 respectively in the omega-3 fatty acids group ($P < 0.01$, < 0.001 , < 0.05 , < 0.05) compared to the baseline. HsCRP and triglyceride reduction were more significant in omega-3 fatty acids group compared to the placebo group ($P = 0.021$ and 0.011 respectively). (2) In the omega-3 fatty acids group, the values and percentage of TG reduction had a significantly positive relation with HsCRP reduction ($r = 0.51$ and 0.45 , $P = 0.021$ and 0.047 respectively). **CONCLUSION:** In CHD and CHD risk equivalent patients with mixed dyslipidemia, dyslipidemia's therapeutic effect using simvastatin and omega-3 fatty acids may result from not only the combination of lipid adjustment, but also enhancement of their own nonlipid influences.

Am J Clin Nutr. 2004 Jun;79(6):974-82.

Moderate fish-oil supplementation reverses low-platelet, long-chain n-3 polyunsaturated fatty acid status and reduces plasma triacylglycerol concentrations in British Indo-Asians.

Lovegrove JA, Lovegrove SS, Lesauvage SV, Brady LM, Saini N, Minihane AM, Williams CM.

BACKGROUND: The mechanisms involved in the increased mortality from coronary artery disease in British Indo-Asians are not well understood. **OBJECTIVES:** This study aimed to investigate whether British Indo-Asian Sikhs have higher plasma triacylglycerol concentrations, lower platelet phospholipid levels, and lower dietary intakes of long-chain n-3 polyunsaturated fatty acids (PUFAs) than do age- and weight-matched Europeans and whether moderate dietary fish-oil intake can reverse these differences. **DESIGN:** A randomized, double-blind, placebo-controlled, parallel, fish-oil intervention study was performed. After a 2-wk run-in period, 44 Europeans and 40 Indo-Asian Sikhs were randomly assigned to receive either 4.0 g fish oil [1.5 g eicosapentaenoic acid (EPA) and 1.0 g docosahexaenoic acid (DHA)] or 4.0 g olive oil (control) daily for 12 wk. **RESULTS:** At baseline, the Indo-Asians had significantly higher plasma triacylglycerol, small dense LDL, apolipoprotein B, and dietary and platelet phospholipid n-6 PUFA values and significantly lower long-chain n-3 PUFAs (EPA and DHA) than did the Europeans. A significant decrease in plasma triacylglycerol, plasma apolipoprotein B-48, and platelet phospholipid arachidonic acid concentrations and a significant increase in plasma HDL concentrations and platelet phospholipid EPA and DHA levels were observed after fish-oil supplementation. No significant effect of ethnicity on the responses to fish-oil supplementation was observed. **CONCLUSIONS:** Moderate fish-oil supplementation contributes to a reversal of lipid abnormalities and low n-3 PUFA levels in Indo-Asians and should be considered as an important, yet simple, dietary manipulation to reduce CAD risk in Indo-Asians with an atherogenic lipoprotein phenotype.

Am J Clin Nutr. 2004 May;79(5):765-73.

Differential eicosapentaenoic acid elevations and altered cardiovascular disease risk factor responses after supplementation with docosahexaenoic acid in postmenopausal women receiving and not receiving hormone replacement therapy.

Stark KD, Holub BJ.

BACKGROUND: Dietary docosahexaenoic acid (DHA) has triacylglycerol-lowering potential and undergoes in vivo retroconversion to eicosapentaenoic acid (EPA) in humans. Hormone replacement therapy (HRT) influences circulating lipid concentrations and fatty acid metabolism. DHA supplementation has not been studied in postmenopausal women. **OBJECTIVE:** We studied the effects of supplementation with DHA (free of EPA) on the resulting elevation in EPA and on selected cardiovascular disease risk factors in postmenopausal women. **DESIGN:** Women receiving ($n = 18$) and not receiving ($n = 14$) HRT completed a randomized, double-blind, placebo-controlled crossover trial with a DHA supplement (2.8 g DHA/d). A washout period of $> \text{or} = 6$ wk divided the two 28-d intervention periods. Fasting blood samples were collected for analysis. **RESULTS:** In all women, DHA supplementation was associated with significant changes ($P < 0.05$), including 20% lower serum triacylglycerol concentrations, 8% higher HDL-cholesterol concentrations, a 28% lower overall ratio of serum triacylglycerol to HDL cholesterol,

and a 7% decrease in resting heart rate. DHA supplementation resulted in a 45% lower net increase ($P = 0.02$) in EPA and a 42% lower ($P = 0.0028$) estimated percentage retroconversion of DHA to EPA [$\Delta\text{EPA}/(\Delta\text{EPA} + \Delta\text{DHA}) \times 100$] in women receiving than in those not receiving HRT. CONCLUSION: With DHA supplementation, the accumulation of EPA in serum phospholipids is significantly attenuated in postmenopausal women receiving HRT compared with that in women not receiving HRT. DHA supplementation can also favorably influence selected cardiovascular disease risk factors in postmenopausal women.

Lipids. 2003 Apr;38(4):353-8.

n-3 long-chain FA decrease serum levels of TG and remnant-like particle-cholesterol in humans.

Hamazaki K, Itomura M, Huan M, Nishizawa H, Watanabe S, Hamazaki T, Sawazaki S, Terasawa K, Nakajima S, Terano T, Hata Y, Fujishiro S.

A large number of papers have reported that administration of n-3 FA reduced serum TG concentrations in hypertriglyceridemic patients. However, few studies have examined the effect of n-3 FA on serum concentrations of remnant-like particle (RLP) cholesterol. Volunteers ($n = 41$) whose serum TG concentrations were 100-300 mg/dL were recruited and randomly assigned to either an n-3 FA group or a control group with stratification by sex, age, and serum TG level in a double-blind manner. The subjects in the n-3 FA group were administered 125 mL of fermented soybean milk with fish oil containing 600 mg of EPA and 260 mg of DHA/d for 12 wk. The controls consumed control soybean milk with olive oil. Fasting blood samples were obtained before the start of administration and at 4, 8, and 12 wk. EPA concentrations in red blood cells increased significantly in all but one subject in the n-3 FA group, with no significant changes in the control group. TG levels decreased more in the n-3 FA group than in the control group at weeks 4 ($P < 0.05$), 8 ($P < 0.01$), and 12 ($P < 0.05$) with their baseline as covariate. RLP cholesterol levels decreased more in the n-3 FA group than in the control at weeks 8 ($P < 0.01$) and 12 ($P < 0.05$) with their baseline as covariate. The groups did not differ in the other lipid levels. It is likely that n-3 long-chain FA may exert anti-atherosclerotic effects by lowering serum TG and RLP-cholesterol levels even at the dose of 860 mg/d.

J Lipid Res. 2003 Mar;44(3):455-63. Epub 2002 Dec 1.

Omega-3 fatty acid supplementation accelerates chylomicron triglyceride clearance.

Park Y, Harris WS.

Omega-3 fatty acids (FAs) reduce postprandial triacylglycerol (TG) concentrations. This study was undertaken to determine whether this effect was due to reduced production or increased clearance of chylomicrons. Healthy subjects ($n = 33$) began with a 4-week, olive oil placebo (4 g/d) run-in period. After a 4-week wash-out period, subjects were randomized to supplementation with 4 g/d of ethyl esters of either safflower oil (SAF), eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA) for 4 weeks. Results for EPA and DHA were similar, and therefore the data were combined into one omega-3 FA group. Omega-3 FA supplementation reduced the postprandial TG and apolipoprotein B (apo B)-48 and apoB-100 concentrations by 16% ($P = 0.08$), 28% ($P < 0.001$), and 24% ($P < 0.01$), respectively. Chylomicron TG half-lives in the fed state were reduced after omega-3 FA treatment (6.0 \pm 0.5 vs. 5.1 \pm 0.4 min; $P < 0.05$), but not after SAF (6.9 \pm 0.7 vs. 7.1 \pm 0.7 min). Omega-3 FA supplementation decreased chylomicron particle sizes (mean diameter; 293 \pm 44 vs. 175 \pm 25 nm; $P < 0.01$) and increased preheparin lipoprotein lipase (LPL; 0.6 \pm 0.1 vs. 0.9 \pm 0.1 micromol/h/ml; $P < 0.05$) activity during the fed state, but had no effect on postheparin LPL or hepatic lipase activities. The results suggest that omega-3 FA supplementation accelerates chylomicron TG clearance by increasing LPL activity, and that EPA and DHA are equally effective.

Am J Clin Nutr. 2003 Feb;77(2):300-7.

Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity.

Chan DC, Watts GF, Mori TA, Barrett PH, Redgrave TG, Beilin LJ.

BACKGROUND: Lipid abnormalities may contribute to the increased risk of atherosclerosis and coronary disease in visceral obesity. Fish oils lower plasma triacylglycerols, but the underlying mechanisms are not fully understood. OBJECTIVE: We studied the effect of fish oils on the metabolism of apolipoprotein B-100 (apo B) and chylomicron remnants in obese men. DESIGN: Twenty-four dyslipidemic, viscerally obese men were randomly assigned to receive either fish oil capsules (4 g/d, consisting of 45% eicosapentaenoic acid and 39% docosahexaenoic acid as ethyl esters) or matching placebo (corn oil, 4 g/d) for 6 wk. VLDL, intermediate-density lipoprotein (IDL), and LDL apo B kinetics were assessed by following apo B isotopic enrichment with the use of gas chromatography-mass spectrometry after an intravenous bolus injection of trideuterated leucine. Chylomicron remnant catabolism was measured with the use of an intravenous injection of a chylomicron remnant-like emulsion containing cholesteryl [(13)C]oleate, and isotopic enrichment of (13)CO(2) in breath was measured with isotope ratio mass spectrometry. Kinetic values were derived with multicompartmental models. RESULTS: Fish oil supplementation

significantly ($P < 0.05$) lowered plasma concentrations of triacylglycerols (-18%) and VLDL apo B (-20%) and the hepatic secretion of VLDL apo B (-29%) compared with placebo. The percentage of conversions of VLDL apo B to IDL apo B, VLDL apo B to LDL apo B, and IDL apo B to LDL apo B also increased significantly ($P < 0.05$): 71%, 93%, and 11%, respectively. Fish oils did not significantly alter the fractional catabolic rates of apo B in VLDL, IDL, or LDL or alter the catabolism of the chylomicron remnant-like emulsion. **CONCLUSION:** Fish oils effectively lower the plasma concentration of triacylglycerols, chiefly by decreasing VLDL apo B production but not by altering the catabolism of apo B-containing lipoprotein or chylomicron remnants.

Am J Clin Nutr. 2003 Jan;77(1):37-42.

Effects of supplementation with fish oil-derived n-3 fatty acids and gamma-linolenic acid on circulating plasma lipids and fatty acid profiles in women.

Laidlaw M, Holub BJ.

BACKGROUND: Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and gamma-linolenic acid (GLA) have lipid-modifying and antiinflammatory properties. The effects of supplement mixtures of these fatty acids on plasma lipids and the fatty acid compositions of serum phospholipids have received little attention. **OBJECTIVE:** The objective was to determine the effects of different levels of GLA supplementation together with a constant intake of EPA plus DHA on the triacylglycerol-lowering effect of EPA plus DHA alone and on the fatty acid patterns (eicosanoid precursors) of serum phospholipids. **DESIGN:** Thirty-one women were assigned to 1 of 4 groups, equalized on the basis of their fasting triacylglycerol concentrations. They received supplements providing 4 g EPA+DHA (4:0, EPA+DHA:GLA; control group), 4 g EPA+DHA plus 1 g GLA (4:1), 2 g GLA (4:2), or 4 g GLA (4:4) daily for 28 d. Plasma lipids and fatty acids of serum phospholipids were measured on days 0 and 28. **RESULTS:** Plasma triacylglycerol concentrations were significantly lower on day 28 than on day 0 in the 4:0, 4:1, and 4:2 groups. LDL cholesterol decreased significantly (by 11.3%) in the 4:2 group. Dihomo-gamma-linolenic acid increased significantly in serum phospholipids only in the 4:2 and 4:4 groups; however, total n-3 fatty acids increased in all 4 groups. **CONCLUSIONS:** A mixture of 4 g EPA+DHA and 2 g GLA favorably altered blood lipid and fatty acid profiles in healthy women. On the basis of calculated PROCAM values, the 4:2 group was estimated to have a 43% reduction in the 10-y risk of myocardial infarction.

Atherosclerosis. 2001 Jul;157(1):131-5.

Effect of dietary omega-3 fatty acids on high-density lipoprotein apolipoprotein AI kinetics in type II diabetes mellitus.

Frenais R, Ouguerram K, Maugeais C, Mahot P, Charbonnel B, Magot T, Krempf M.

The effect of a dietary fish oil supplementation on metabolism of HDL was studied in type II diabetes mellitus. Endogenous labeling of HDL-apo AI was performed using a 14 h primed infusion of D3-leucine in five diabetic patients before and 2 months after treatment with maxEPA(R). Isotopic enrichment curves were analyzed using a monoexponential function. After treatment, plasma cholesterol level remained unchanged (205.4±41.9 vs. 206.8±30.7 mg/dl, NS), whereas plasma triglycerides were decreased (155.4±67.9 vs. 202.6±32.2 mg/dl, $P=0.06$). Plasma apo AI was similar under maxEPA(R) (116.0±25.6 vs. 111.8±25.4 mg/dl, NS), and HDL-cholesterol and HDL-triglycerides were also not markedly changed (30.2±10.0 vs. 27.1±10 mg/dl, and 15.3±9.8 vs. 19.2±10.4 mg/dl, NS). HDL-apo AI fractional catabolic rate (FCR) and absolute production rate (APR) were significantly decreased after treatment with maxEPA(R) (0.27±0.09 vs. 0.37±0.08 pool day, $P<0.05$, and 12.1±2.8 vs. 16.1±3.3 mg/kg per day, $P<0.05$). These findings showed an effect of maxEPA(R) on kinetics of apolipoprotein AI in type II diabetes mellitus, probably linked to changes in plasma triglyceride level

Am J Clin Nutr. 2001 Jul;74(1):50-6.

Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol.

Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L.

BACKGROUND: Results of epidemiologic studies and clinical trials indicate that moderate doses of n-3 fatty acids reduce the risk of cardiovascular disease and may improve prognosis. **OBJECTIVE:** The objective was to evaluate the effect of a high-dose ethylester concentrate of n-3 fatty acids administered early after an acute myocardial infarction (MI) on subsequent cardiac events and serum lipids. **DESIGN:** Three hundred patients with acute MI were randomly assigned to a daily dose of either 4 g highly concentrated n-3 fatty acids or corn oil, administered in a double-blind manner over 12-24 mo. Median follow-up time was 1.5 y. Clinical follow-up, including the drawing of blood samples, was performed after 6 wk of treatment and later at 0.5-year intervals. **RESULTS:** Forty-two (28%) patients in the n-3 group and 36 (24%) in the corn oil group experienced at least

one cardiac event (cardiac death, resuscitation, recurrent MI, or unstable angina). No significant difference in prognosis was observed between groups for single or combined cardiac events. Total cholesterol concentrations decreased in both groups, with no significant intergroup differences. On average, the monthly increase in HDL cholesterol was 1.11% in the n-3 group and 0.55% in the corn oil group ($P = 0.0016$). Triacylglycerol concentrations decreased by 1.30%/mo in the n-3 group, whereas they increased by 0.35%/mo in the corn oil group ($P < 0.0001$). CONCLUSION: No clinical benefit of a high-dose concentrate of n-3 fatty acids compared with corn oil was found despite a favorable effect on serum lipids.

Pak J Pharm Sci. 2000 Jan;13(1):1-11.

A comparative study of omega-3-fatty acids obtained from marine fish and bezafibrate alone and in combination as hypolipidemic agents.

Saify ZS, Hassan S, Arif M, Ahmad F, Chishti KA, Siddiqui S.

The fish oil and its constituents have been studied in detail with special reference to ailments. The discovery of omega-3 fatty acids led to a detailed investigation about its effect and role as anti-cholesterolemic agents. The effect of fish oil alone and in combination with acid derivatives was found to be a potent cholesterol and triglycerides lowering agent. Comparative studies of fish oils and bezafibrate led to the formulation of new therapeutic combination having lesser side effects and toxicity.

J Nutr Biochem. 1999 Mar;10(3):151-8.

Omega-3 fatty acids alter lipoprotein subfraction distributions and the in vitro conversion of very low density lipoproteins to low density lipoproteins.

Lu G, Windsor SL, Harris WS.

The purpose of this study was to determine the effects of a fish oil concentrate (FOC) on the in vitro conversion of very low density lipoproteins (VLDL) to intermediate (IDL) and low density lipoproteins (LDL). Six hypertriglyceridemic patients were randomly allocated to receive either placebo (olive oil) or FOC (1 g/14 kg body weight/day) for 4 weeks in a crossover study with a 4-week washout period. The FOC provided 3 g of eicosapentaenoic + docosahexaenoic acid per 70 kg of body weight, and it lowered plasma triglyceride and VLDL cholesterol levels by 35% and 42%, respectively. Decreases in the largest particles (VLDL(1)) were primarily responsible, with no effect noted in smaller VLDL particles (VLDL(2) and VLDL(3)). The FOC increased LDL cholesterol levels by 25% ($P < 0.06$) but did not affect LDL particle size. VLDL(1) and VLDL(3) were incubated in vitro with human postheparin lipases. Although triglycerides from both types of VLDL were hydrolyzed to the same extent with both treatments, particles isolated during the FOC phase were more readily converted into IDL and LDL than were control particles. These data suggest that the marine omega3 fatty acids may enhance the propensity of VLDL to be converted to LDL, partly explaining the decreased VLDL and increased LDL levels in FOC-treated patients.

Rev Esp Fisiol. 1997 Dec;53(4):349-54.

Heterogeneous responsiveness of normolipemic women to n-3 long chain fatty acid supplementation. Changes in serum lipids and apoproteins.

Sanchez-Muniz FJ, Bastida S, Quintas E, Merinero MC, Rodriguez-Gil S.

The effect of 10 day-low dosage of n-3 long chain fatty acids (390 mg/day of EPA and 252 mg/day of DHA) on lipid and apolipoprotein (Apo) concentrations has been studied in nine normolipidaemic women aged 28.9 +/- 4.2 years. n-3 fatty acid supplementation did not significantly decrease total cholesterol and triglyceride levels but markedly decreased the Apo A1 and Apo B concentrations (12.7%, $p < 0.01$ and 23.1%, $p < 0.001$, respectively), while the Apo A1/Apo B ratio significantly increased (14.8%, $p < 0.02$). In contrast to the individual variations found for triglycerides and cholesterol, Apo changes indicate a fairly homogeneous response to the fish oil supplement. In seven women Apo A1 decreased (> 10%), whereas Apo B decreased (> 10%) in all of them. The Apo A1/Apo B ratio increased (> 10%) in five of these nine women. Changes in Apo A-1 and Apo B did not significantly correlate with changes in serum lipids. These findings suggest that short-term supplementation with low amount of n-3 long chain fatty acids, EPA and DHA, influences the serum Apo content more than the lipid levels in normolipidaemic women.

Diabetologia. 1997 Jan;40(1):45-52.

Effect of omega 3 fatty acid on plasma lipids, cholesterol and lipoprotein fatty acid content in NIDDM patients.

Goh YK, Jumpsen JA, Ryan EA, Clandinin MT.

This study was conducted to examine the effect of omega 3 fatty acid supplementation on plasma lipid, cholesterol and lipoprotein fatty acid content of non-insulin-dependent diabetic individuals consuming a higher (0.65, n = 10) or lower (0.44, n = 18) ratio of dietary polyunsaturated to saturated fatty acid (P/S). The participants were initially given an olive oil supplement (placebo) equivalent to 35 mg of 18:1. kg body weight⁻¹.day⁻¹ for 3 months. This was followed by two omega 3 supplement periods in a randomized crossover. In these 3-month periods, participants were given a linseed oil supplement equivalent to 35 mg of 18:3 omega 3.kg body weight⁻¹.day⁻¹ or a fish oil supplement equivalent to 35 mg of 20:5 omega 3 + 22:6 omega 3.kg body weight⁻¹. day⁻¹. At the end of each supplement period, a blood sample was drawn from each participant for lipid, lipoprotein, insulin, glucagon and C-peptide analyses. At the end of each 3-month period a 7-day dietary record was completed to calculate dietary fat intake and P/S ratio. Results indicate that fish oil significantly reduced plasma triacylglycerol level (p < 0.05) and increased 20:5 omega 3 and 22:6 omega 3 content of all lipoprotein lipid classes. Linolenic acid supplementation had no effect on plasma triacylglycerol level, but it increased 18:3 omega 3 content of lipoprotein cholesterol ester fractions (p < 0.05). A slight increase in 20:5 omega 3, but not 22:6 omega 3, content was noted in lipoprotein lipid classes as a result of 18:3 omega 3 supplementation. LDL and HDL cholesterol, insulin, glucagon and C-peptide levels were not affected by either omega 3 supplement. It is concluded that a modest intake of omega 3 fatty acids, such as could be obtained from consuming fish regularly, will reduce plasma triglyceride level without affecting LDL or HDL cholesterol levels.

Z Ernährungswiss. 1996 Jun;35(2):191-8.

[Effect of low dose omega-3 fatty acid supplementation on plasma lipids and lipoproteins in coronary patients with dyslipoproteinemia]

Schindler OS, Rost R.

In a prospective study, 20 patients (aged 48-67 years) with primary hyperlipoproteinaemia of phenotypes IIa, IIb, IV and with proven coronary sclerosis received four different doses of long-chain polyunsaturated omega-3 fatty acids. 0.18 to 1.1 g per day were administered in the form of fish oil capsules over four 2-week periods. The aim was to study the effect of different low dose supplementations of n-3 fatty acids on the plasmalipid- and lipoprotein composition and to determine a threshold of effectiveness. Significant reduction of the triglyceride level was registered in all subjects with the greatest decrease in those patients who presented with the highest base levels. The cholesterol and LDL-cholesterol values on average remained almost unchanged, apart from a significant increase of LDL-cholesterol in patients with type IV hyperlipoproteinaemia. The HDL-cholesterol fraction also showed a significant increase in type IIb patients which was related to alterations of the HDL-3 subfraction. The minimal effective dose of a daily administration of omega-3 fatty acids can be expected between 0.18 g and 0.35 g. The observed changes of plasmalipids and lipoproteins reflect the beneficial effect of long-chain polyunsaturated omega-3 fatty acids in respect to plasma-triglyceride reduction and HDL-cholesterol increase as seen in other studies, despite the use of supplementations far below 1 g per day.

J Intern Med. 1995 Mar;237(3):249-59.

Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia.

Grundt H, Nilsen DW, Hetland O, Aarsland T, Baksaas I, Grande T, Woie L.

OBJECTIVES. To investigate the effect of an omega-3 fatty acid concentrate K85 on serum lipids, lipoproteins, insulin metabolism and blood pressure in subjects with combined hyperlipidaemia. **DESIGN.** After a run-in dietary period of 10 weeks, subjects were randomly allocated to receive either encapsulated K85 (n = 28) or corn oil (n = 29). The intervention was double-blind. **SETTING.** An outpatient centre in Stavanger, Norway. **SUBJECTS.** Fifty-seven of 141 individuals, who, after the run-in period continued to meet the inclusion criteria: serum triglycerides of > or = 2.0 mmol L⁻¹ and total serum cholesterol of > or = 6.0 mmol L⁻¹. **INTERVENTION.** Encapsulated K85, containing 85% eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), or corn oil, both administered in a daily dose of 4 g for 12 weeks. **MAIN OUTCOME MEASURES.** Change in metabolic and haemodynamic parameters related to intervention. **RESULTS.** Serum EPA and DHA increased significantly in the K85 group during the treatment period. The body-mass index remained unchanged. A 28% reduction in serum triglycerides was noted in the K85 group from the first 4 weeks. Total serum cholesterol was significantly reduced with both regimens. Serum high-density lipoprotein cholesterol increased significantly during the first 8 weeks in the K85 group. Significant reductions in systolic and diastolic blood pressures were noted in subjects on K85. The treatment did not affect serum glucose, plasma insulin and proinsulin levels. Insulin:glucose and proinsulin:glucose ratios remained unchanged. **CONCLUSIONS.** The atherogenic risk profile was improved with K85 in subjects with combined hyperlipidaemia, but n-3 fatty acids supplementation did not affect glucose/insulin homeostasis.

Scand J Clin Lab Invest. 1994 Jul;54(4):273-80.

Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H,

Torjesen PA.

The long-term influence of n-3 polyunsaturated fatty acids (n-3 PUFAs) on serum lipids and glucose homeostasis was studied in a group of non-diabetic, moderately hypertriglyceridaemic patients undergoing coronary artery bypass grafting. They were investigated according to the same procedure before and 6 months after the operation. Following randomization postoperatively, 28 patients received 3.4 g eicosapentaenoic and docosahexaenoic acid per day, whereas 29 patients comprised the control group. The decline in serum triglycerides after 6 months was significantly greater in the n-3 PUFA group than in the control group (median decline, -33.2% vs. -11.1%, $p = 0.002$), while no group difference was noted in serum total, HDL, or LDL cholesterol levels. Fasting plasma glucose levels decreased less in the n-3 PUFA group compared with the control group (median change, -0.2 mmol l⁻¹ vs. -0.5 mmol l⁻¹, $p = 0.054$). The corresponding changes in fasting insulin levels were -2 mIU ml⁻¹ in the n-3 PUFA group and no change in the control group ($p = 0.039$). In both groups combined, the recorded changes in serum triglyceride and serum insulin levels were negatively correlated with the change in serum phospholipid n-3 fatty acids ($r = -0.35$, $p = 0.008$ and $r = -0.32$, $p = 0.016$, respectively). An oral glucose tolerance test revealed no significant group differences after 6 months, neither in the peak levels, nor in the areas under the curves between 0 and 3h after the glucose load for glucose, insulin, and C-peptide.

Lipids. 1994 Feb;29(2):145-7.

The acute effects of a single very high dose of n-3 fatty acids on plasma lipids and lipoproteins in healthy subjects.

Svaneborg N, Moller JM, Schmidt EB, Varming K, Lervang HH, Dyerberg J.

Forty healthy volunteers were allocated in a double blind, randomized study to receive either 20 g of n-3 polyunsaturated fatty acids (PUFA) or 20 g of n-6 PUFA at their evening meal. The effect on plasma lipids and lipoproteins of this single dose of fish oil vs. corn oil was studied the next morning, 14 h after ingestion. Plasma triglycerides and very low density lipoprotein-cholesterol significantly decreased (33%) after n-3 PUFA ($P < 0.001$), and significantly ($P < 0.01$) more than after intake of n-6 PUFA. The decrease in plasma triglycerides after n-3 PUFA ingestion was more pronounced in subjects with higher baseline levels of triglycerides ($P < 0.001$). Total cholesterol decreased after both supplements, but did not differ between the supplements. Low density lipoprotein-cholesterol did not change, and high density lipoprotein-cholesterol significantly decreased in subjects given n-3 PUFA compared to baseline, but not when compared to subjects receiving n-6 PUFA. In conclusion, we have shown that a single very high dose of n-3 PUFA has a pronounced hypotriglyceridemic effect, which is directly related to the initial plasma level.

Arterioscler Thromb. 1993 Dec;13(12):1755-62.

Effect of pravastatin and omega-3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia.

Contacos C, Barter PJ, Sullivan DR.

This study compared the effects of a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, fish oil, and placebo on plasma lipids and lipoproteins in patients with mixed hyperlipidemia. After an initial run-in phase, 32 patients were randomized for 6 weeks to either (1) pravastatin 40 mg/d, $n = 10$; (2) fish oil (himega 6 g/d, equivalent to 3 g omega-3 fatty acids/d), $n = 10$; or (3) placebo. After single drug therapy, in the pravastatin group mean total plasma cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein (apo) B fell significantly by 23% ($P < .001$), 30% ($p < .001$), and 26% ($P < .01$), respectively. LDL Stokes' diameter did not change. In the fish oil group mean plasma triglycerides (TG) fell 30% ($P < .05$), LDL Stokes' diameter increased from 25.0 to 25.9 nm ($P < .05$), and there was a nonsignificant increase in LDL-C. There were no changes in the placebo group. To assess the effect of the combination of pravastatin plus fish oil therapy, all patients, except one woman from the placebo group who developed nausea on fish oil, then took combined therapy of pravastatin 40 mg/d plus fish oil 6 g/d for an additional 12 weeks. In each case, there were no clinically significant episodes of muscle tenderness or elevation of creatine phosphokinase or alanine aminotransferase. After 12 weeks of combined therapy of pravastatin plus fish oil, there were significant reductions in the mean TC, TG, LDL-C, and apoB in the three groups compared with baseline levels.

Atherosclerosis. 1993 Nov;103(2):107-21.

The effects of n-3 fatty acids on plasma lipids and lipoproteins and other cardiovascular risk factors in patients with hyperlipidemia.

Schmidt EB, Kristensen SD, De Caterina R, Illingworth DR.

This review discusses the effects of dietary n-3 fatty acids on the plasma concentrations and metabolism of lipoproteins with a particular focus on work in human subjects. The influence of dietary n-3 fatty acids on the concentrations of plasma lipoproteins are affected by the amount of n-3 fatty acids as well as by the lipoprotein phenotype in the patients under investigation. On the basis of the observed changes in lipoproteins, dietary n-3 fatty acids exert the greatest effects on the concentrations of triglyceride-rich lipoproteins; their therapeutic potential is greatest in patients with hypertriglyceridemia. In addition to their effects on plasma lipoproteins, dietary n-3 fatty acids have been reported to exert potentially favorable effects on blood pressure, platelet function and viscosity. These effects may justify the use of supplements of dietary n-3 fatty acids in selected patients with hypertriglyceridemia to reduce the risk of atherosclerosis; however, the benefits of such therapy remain to be demonstrated.

Lipids. 1992 Jul;27(7):533-8.

Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years.

Saynor R, Gillott T.

The present study was designed to assess the effectiveness of the n-3 fatty acids in modifying serum total, low density lipoprotein and high density lipoprotein (HDL) cholesterol, as well as serum triglycerides, over a seven-year period. Changes in plasma fibrinogen were recorded and long term safety assessed. A total of 365 subjects with ischemic heart disease (IHD), hyperlipidemia or a strong family history of IHD had their diet supplemented with MaxEPA (Seven Seas Ltd., Hull, England) fish oil containing 18-19% eicosapentaenoic acid. Venous blood samples were taken at regular intervals for lipid and fibrinogen assays and routine clinical chemistry and hematological profiling. Current medication was recorded and no further dietary modification was attempted. Triglyceride and fibrinogen were significantly reduced, whereas a significant reduction in total cholesterol occurred only in the subjects with a pre-oil level greater than 6.5 mmol/L. HDL cholesterol significantly increased over the study period. Clinical chemistry and hematological profiles were not adversely affected, and platelet count did not change significantly. The type of lipid changes observed were those usually considered antiatherogenic. Reducing fibrinogen may result in beneficial changes in the pathological processes leading to thrombotic occlusion. The consumption of MaxEPA by our patients over a seven-year period did not indicate any adverse effects.

Thromb Haemost. 1990 Feb 19;63(1):1-5.

Dose-response studies on the effect of n-3 polyunsaturated fatty acids on lipids and haemostasis.

Schmidt EB, Varming K, Ernst E, Madsen P, Dyerberg J.

We have studied the dose-response effects of dietary supplementation with n-3 polyunsaturated fatty acids (n-3 PUFA's) on lipids and haemostasis. Ten healthy males were each given 1.3 g, 4 g or 9 g of n-3 PUFA's daily for 6-week periods. Bleeding time, HDL-cholesterol and plasminogen activator inhibitor increased with the dose of n-3 PUFA. Plasma fibrinogen and triglyceride levels were reduced in a dose-dependent fashion. After ingestion of 1.3 g of n-3 PUFA's plasma fibrinogen decreased from 9 to 7 $\mu\text{mol/l}$ and HDL-cholesterol increased from 1.2 to 1.3 mmol/l. The bleeding time was prolonged from 5 to 6.5 min while triglyceride levels decreased from 1.2 to 0.9 mmol/l after ingestion of 4 g of n-3 PUFA's. Dietary supplementation with the highest daily dose (9 g) reduced plasma levels of triglycerides, fibrinogen and von Willebrand factor, while bleeding time, plasminogen activator antigen, plasminogen activator inhibitor and the ratio of HDL-cholesterol to total cholesterol increased.

Thromb Res. 1989 Mar 1;53(5):467-74.

Influence of highly concentrated n-3 fatty acids on serum lipids and hemostatic variables in survivors of myocardial infarction receiving either oral anticoagulants or matching placebo.

Smith P, Arnesen H, Opstad T, Dahl KH, Eritsland J.

Forty patients with previous myocardial infarction were given 4 capsules with 1 g concentrated fish oil preparation daily for 4 weeks. No special diet was applied. The supplementation was equivalent to 3.4 grams of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily. Twenty-two of the 40 subjects received concomitant treatment with long-term oral anticoagulants (OAC). The fatty acid composition of serum after the supplementation period showed a significant increase in

the proportion of EPA and DHA, while arachidonic acid (AA) remained essentially constant. This resulted in a rise of the EPA/AA ratio from 0.59 to 1.49 (p less than 0.001), confirming satisfying absorption of the concentrate. Blood lipids showed an overall decrease of triglycerides (TG) by 25% ($p = 0.02$), while total cholesterol rose by 5% ($p = 0.03$) and HDL-cholesterol was unaffected. Blood glucose and the TG associated factors plasminogen activator inhibitor and factor VII-phospholipid complex revealed trends towards reduction. Ivy bleeding time showed a significant prolongation, the median increasing from 240 to 270 seconds. A significant increase of fibrinogen was seen, as was a decrease of clotting time in the combined prothrombin test in patients receiving concomitant OAC. Thus, given for 4 weeks, the investigated concentrate of n-3 fatty acids exerts not merely beneficial effects as far as the risk profile for atherosclerotic disease is concerned. The results also point towards interactions with OAC that may be of clinical relevance.(ABSTRACT TRUNCATED AT 250 WORDS)

J Intern Med Suppl. 1989;731:99-104.

Influence of n-3 fatty acids on blood lipids in normal subjects.

Sanders TA, Hinds A, Pereira CC.

The effects of consuming oils providing alpha-linolenic (ALA), eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids were studied in healthy volunteers. A blunted increase in plasma triglyceride was observed in subjects given a test meal containing fish oil compared with olive oil; cholesterol concentrations were not increased; increases in EPA and DHA were seen in all lipid fractions. In longer term supplementation studies, ALA increased EPA, but not DHA in plasma phospholipids; preformed EPA was more effective. The proportion of EPA in platelet lipids increased in a dose dependent manner. EPA or DHA, but not ALA, decreased plasma triglyceride and VLDL cholesterol concentrations. Supplements containing DHA increased HDL and HDL2 cholesterol and LDL apoB. Total cholesterol and LDL cholesterol concentrations were unaltered.

J Clin Invest. 1985 Oct;76(4):1626-31.

Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans.

von Schacky C, Fischer S, Weber PC.

We studied the incorporation and metabolism of eicosapentaenoic (EPA) and docosahexaenoic acid in six human volunteers who supplemented their normal Western diet for 5 mo daily with 10-40 ml of cod liver oil, rich in omega-3 polyunsaturated fatty acids. EPA and docosahexaenoic acid were incorporated into the total phospholipids of plasma, platelets, and erythrocytes in a dose- and time-dependent manner. During omega-3 fatty acid ingestion serum triacylglycerols were lowered and platelet aggregation upon low doses of collagen was reduced. Concomitantly, formation and excretion of prostanoids showed a characteristic change. As measured in serum from whole clotted blood, thromboxane A₃ was formed in small amounts, whereas thromboxane A₂ formation was reduced to 50% of control values. Excretion of the main urinary thromboxane A metabolites was unaltered in subjects with low basal excretion rates, but decreased markedly in two subjects with high control values. As determined from the main urinary metabolite, prostaglandin I₃ was formed from EPA at rates up to 50% of unaltered prostaglandin I₂ formation. The biochemical and functional changes observed lasted for the entire supplementation period of 5 mo and were reversible within 12 wk after cessation of cod liver oil intake. Favorable changes induced by long-chain omega-3 fatty acids include a dose-related and sustained shift of the prostaglandin I/thromboxane A balance to a more antiaggregatory and vasodilatory state.

Thromb Haemost. 1983 Aug 30;50(2):543-6.

The effect of N-6 and N-3 polyunsaturated fatty acids on hemostasis, blood lipids and blood pressure.

Mortensen JZ, Schmidt EB, Nielsen AH, Dyerberg J.

Diverging results from studies of marine oil supplementation to western diets initiated the undertaking of a double-blind crossover study, with administration to healthy volunteers for 4 weeks of either 10 g of fish oil or 10 g of vegetable oil. Each oil containing approx. 40% of n-3 and n-6 polyunsaturated fatty acids (PUFA) respectively. During the n-3 PUFA period, systolic blood pressure, plasma total lipids, triglycerides and VLDL concentrations fell significantly whereas plasma antithrombin-III (AT-III) rose. Cutaneous bleeding time increased significantly. In contrast only AT-III rose during the n-6 PUFA feeding, however, more marked than during the n-3 oil period. It is concluded that a n-3 PUFA oil supplement to the western diet exerts an effect that generally is considered as beneficial in terms of the risk of developing cardiovascular diseases. It is in this respect superior to that of n-6 PUFA, stressing the necessity of a more differentiated approach to advice on dietary PUFA enrichment than presently is exerted.

ProThera, Inc.
10439 Double R Blvd
Reno, NV 89521
Phone Toll-Free 1-888-488-2488
www.protherainc.com