

Fish Oil and Metabolic Syndrome

Med Sci Monit. 2005 Dec;11(12):RA359-67. Epub 2005 Nov 24.

Dietary fats, fatty acids and insulin resistance: short review of a multifaceted connection.

Haag M, Dippenaar NG.

Insulin resistance is a growing worldwide phenomenon, which progressively develops over years, and finally, if unchecked, predisposes to cardiovascular disease and diabetes mellitus type 2. Insulin resistance is a generalized metabolic disorder characterized by inefficient insulin function in skeletal muscle, liver and adipocytes. There is growing evidence that an increased free fatty acid level, and more importantly, the relative amounts of saturated and unsaturated fatty acids contributing to it, plays an important role in the development of insulin resistance. In turn, this is a reflection of the composition of dietary fat. Ultimately both the dietary intake and plasma levels determine the fatty acid composition of cell membranes. Higher levels of membrane saturated fatty acids seem to greatly impair the action of insulin, whereas the presence of polyunsaturated fatty acids, especially of the omega-3 and -6 families, in contrast, improves insulin sensitivity. In vitro studies, however, have not always corroborated the clinical evidence. Possible roles played by the various saturated and unsaturated fatty acids in the insulin-signaling pathway are discussed in light of recent evidence. Fatty acids have also been shown to alter gene expression in cells, in particular the peroxisome proliferator-activated receptor-gamma2 gene, adding to this multifaceted connection. As man has moved over the centuries from a hunter-gatherer diet to greater intakes of saturated and trans-fatty acids, insulin resistance has appeared with its related pathology. Greater understanding of the role played by dietary fat and plasma fatty acids in pathogenesis of insulin resistance, will allow for more timely prevention and improved treatment in the future.

Int J Circumpolar Health. 2005 Sep;64(4):396-408.

Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan Eskimos: the Alaska Siberia project.

Ebbesson SO, Risica PM, Ebbesson LO, Kennish JM, Tejero ME.

OBJECTIVES: To test the hypothesis that the unusually low prevalences of insulin resistance (IR), metabolic syndrome (MS) and diabetes (DM) in Alaskan Eskimos, compared to American Indians, is related to the traditional Eskimo diet, high in C20-C22 omega-3 fatty acids (FAs). To determine if the relatively low blood pressures, low serum triglycerides and high HDL cholesterol levels in Eskimos result from high omega-3 FA consumption. **STUDY DESIGN:** Cross-sectional study. **METHODS:** We measured plasma FA concentrations in 447 Norton Sound Eskimos (35-74 years of age) and screened for DM, CHD and associated risk factors. A dietary assessment (24-hr recall) was obtained for comparison the day before the blood sampling. **RESULTS:** Plasma omega-3 FA concentrations were highly correlated with dietary omega-3 FAs and HDL levels and inversely correlated with plasma levels of insulin, 2-h insulin (OGTT), HOMI-IR, 2-h glucose (OGTT), triglyceride levels and diastolic blood pressure. **CONCLUSIONS:** High consumption of omega-3 FAs positively affects components of the MS, insulin sensitivity and glucose tolerance. This finding suggests that high consumption of C20-C22 omega-3 FAs protects against the development of the MS and glucose intolerance.

Biochim Biophys Acta. 2005 Mar 21;1733(1):67-75.

Substituting dietary linoleic acid with alpha-linolenic acid improves insulin sensitivity in sucrose fed rats.

Ghafoorunissa, Ibrahim A, Natarajan S.

This study describes the effect of substituting dietary linoleic acid (18:2 n-6) with alpha-linolenic acid (18:3 n-3) on sucrose-induced insulin resistance (IR). Wistar NIN male weanling rats were fed casein based diet containing 22 energy percent (en%) fat with approximately 6, 9 and 7 en% saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) respectively for 3 months. IR was induced by replacing starch (ST) with sucrose (SU). Blends of groundnut, palmolein, and linseed oil in different proportions furnished the following levels of 18:3 n-3 (g/100 g diet) and 18:2 n-6/18:3 n-3 ratios respectively: ST-220 (0.014, 220), SU-220 (0.014, 220), SU-50 (0.06, 50), SU-10 (0.27, 10) and SU-2 (1.1, 2). The results showed IR in the sucrose fed group (SU-220) as evidenced by increase in fasting plasma insulin and area under the

curve (AUC) of insulin in response to oral glucose load. In SU-220, the increase in adipocyte plasma membrane cholesterol/phospholipid ratio was associated with a decrease in fluidity, insulin stimulated glucose transport, antilipolytic effect of insulin and increase in basal and norepinephrine stimulated lipolysis in adipocytes. In SU-50, sucrose induced alterations in adipocyte lipolysis and antilipolysis were normalized. However, in SU-2, partial corrections in plasma insulin, AUC of insulin and adipocyte insulin stimulated glucose transport were observed. Further, plasma triglycerides and cholesterol decreased in SU-2. In diaphragm phospholipids, the observed dose dependent increase in long chain (LC) n-3 PUFA was associated with a decrease in LC-n-6 PUFA but insulin stimulated glucose transport increased only in SU-2. Thus, this study shows that the substitution of one-third of dietary 18:2 n-6 with 18:3 n-3 (SU-2) results in lowered blood lipid levels and increases peripheral insulin sensitivity, possibly due to the resulting high LCn-3 PUFA levels in target tissues of insulin action. These findings suggest a role for 18:3 n-3 in the prevention of insulin resistant states. The current recommendation to increase 18:3 n-3 intake for reducing cardiovascular risk may also be beneficial for preventing IR in humans.

Cas Lek Cesk. 2005;144(11):737-41.

[Effect of n-3 polyunsaturated fatty acids on plasma lipid, LDL lipoperoxidation, homocysteine and inflammation indicators in diabetic dyslipidemia treated with statin + fibrate combination]

[Article in Czech]

Zeman M, Zak A, Vecka M, Tvrzicka E, Pisarikova A, Stankova B.

BACKGROUND: The aim of the study was to determine how addition of n-3 polyenic fatty acids (PUFA) to the present treatment with statin + fibrate combination in diabetic dyslipidemia affects plasma lipids and lipoproteins, LDL lipoperoxidation, glucose homeostasis, concentration of serum homocysteine and selected inflammation indicators. **METHODS AND RESULTS:** 24 patients with type 2 diabetes, who after the combined hypolipidemic treatment (pravastatin 20 mg + micronized fenofibrate 200 mg per day) cannot reach the recommended target values for long time, received for three consecutive months supplementation of 3,6 g PUFA n-3 per day or a placebo (olive oil). At the beginning of the study, after three months of PUFA supplementation and after another three months of placebo administration, concentrations of plasma lipids, composition of fatty acids, plasma phosphatidylcholine (PC), cholesterol esters (CE) and triglycerides (TG), concentration of tHcy, conjugated dienes (CD) in LDL and selected inflammation indicators (IL-6, TNFalpha, VCAM-1) were determined. n-3 PUFA supplementation resulted in the significant decrease of tHcy concentration (-29%, $P < 0.01$) and TG (-28%, $P < 0.05$) in plasma. During the period of placebo administration, values returned to base line levels. CD concentration in LDL after n-3 PUFA increased by 15% ($P < 0.15$, not significant), meanwhile after the placebo containing oleic acid it decreased by 18% ($P < 0.05$). **CONCLUSIONS:** Our results show that n-3 PUFA supplementation together with statin + fibrate combination in DDL patients can significantly decrease the risk of cardiovascular diseases.

J Am Diet Assoc. 2005 Mar;105(3):428-40.

n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review.

Nettleton JA, Katz R.

Historically, epidemiologic studies have reported a lower prevalence of impaired glucose tolerance and type 2 diabetes in populations consuming large amounts of the n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) found mainly in fish. Controlled clinical studies have shown that consumption of n-3 LC-PUFAs has cardioprotective effects in persons with type 2 diabetes without adverse effects on glucose control and insulin activity. Benefits include lower risk of primary cardiac arrest; reduced cardiovascular mortality, particularly sudden cardiac death; reduced triglyceride levels; increased high-density lipoprotein levels; improved endothelial function; reduced platelet aggregability; and lower blood pressure. These favorable effects outweigh the modest increase in low-density lipoprotein levels that may result from increased n-3 LC-PUFA intake. Preliminary evidence suggests increased consumption of n-3 LC-PUFAs with reduced intake of saturated fat may reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes in overweight persons. Reported improvements in hemostasis, slower progression of artery narrowing, albuminuria, subclinical inflammation, oxidative stress, and obesity require additional confirmation. Expected health benefits and public health implications of consuming 1 to 2 g/day n-3 LC-PUFA as part of lifestyle modification in insulin resistance and type 2 diabetes are discussed.

Curr Diab Rep. 2004 Oct;4(5):330-4.

Combination therapy of dyslipidemia in non-insulin-dependent diabetes mellitus and the metabolic syndrome.

Rembold CM.

Non-insulin-dependent diabetes mellitus (NIDDM) and the metabolic syndrome separately and additively increase the risk for atherosclerotic cardiovascular disease. Considering the high cardiovascular risk associated with NIDDM and the metabolic syndrome, aggressive therapy of dyslipidemia with tailored combination therapy should be considered given informed consent and discussion of risks. In addition to statins, niacin, and fibrates, therapies shown to decrease the risk for atherosclerotic cardiovascular disease include omega-3 fatty acids, diet, exercise, and optimal blood pressure control with thiazides and blockers of the renin-angiotensin system. These therapies should also be considered to reduce the high cardiovascular risk associated with NIDDM and the metabolic syndrome.

J Nutr Biochem. 2004 Jun;15(6):350-7.

Effects of fish oil on hypertension, plasma lipids, and tumor necrosis factor-alpha in rats with sucrose-induced metabolic syndrome.

Aguilera AA, Diaz GH, Barcelata ML, Guerrero OA, Ros RM.

Dietary fish oil rich in (n-3) fatty acids plays an important role in reducing abnormalities associated with the metabolic syndrome and mortality from coronary heart disease. We investigated the effects of dietary fish oil on the metabolic syndrome in a high-sucrose-fed rat model. The model was achieved by the administration of 30% sucrose in drinking water in male Wistar rats during 21 weeks. After the metabolic syndrome rat model was established, fish oil was administered during 6 weeks. The metabolic syndrome rats showed significant increases in body weight, systolic blood pressure, serum insulin, total lipids, triacylglycerols, cholesterol, free fatty acids, LDL, total proteins, albumin, and serum tumor necrosis factor-alpha (TNF-alpha). They also presented abdominal and epididymal fat accumulation and fatty liver. After fish oil diet administration, metabolic syndrome rats had a significant reduction in blood pressure, serum insulin, triacylglycerols, cholesterol, free fatty acids, and total lipids, but no change was observed in TNF-alpha concentration or fat accumulation. In conclusion, fish oil reversed the alterations on metabolic parameters and blood pressure exerted by sucrose administration, although it had no effect on TNF-alpha production and adiposity. This confirms the theory that the molecular etiology of the metabolic syndrome is multifactorial, as is the effect of n-3 polyunsaturated fatty acids (PUFAs) upon it, having complex and multifaceted actions.

Reprod Nutr Dev. 2004 May-Jun;44(3):289-99.

N-3 long chain polyunsaturated fatty acids: a nutritional tool to prevent insulin resistance associated to type 2 diabetes and obesity?

Delarue J, LeFoll C, Corporeau C, Lucas D.

n-3 long chain polyunsaturated fatty acids (n-3 LC-PUFA), mainly eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), are present in mammal tissues both from endogenous synthesis from desaturation and elongation of 18:3 n-3 and/or from dietary origin (marine products and fish oils). In rodents in vivo, n-3 LC-PUFA have a protective effect against high fat diet induced insulin resistance. Such an effect is explained at the molecular level by the prevention of many alterations of insulin signaling induced by a high fat diet. Indeed, the protective effect of n-3 LC-PUFA results from the following: (a) the prevention of the decrease of phosphatidyl inositol 3' kinase (PI3 kinase) activity and of the depletion of the glucose transporter protein GLUT4 in the muscle; (b) the prevention of the decreased expression of GLUT4 in adipose tissue. In addition, n-3 LC-PUFA inhibit both the activity and expression of liver glucose-6-phosphatase which could explain the protective effect with respect to the excessive hepatic glucose output induced by a high fat diet. n-3 LC-PUFA also decrease muscle intramyofibrillar triglycerides and liver steatosis. This last effect results on the one hand, from a decreased expression of lipogenesis enzymes and of delta 9 desaturase (via a depleting effect on sterol response element binding protein 1c (SREBP-1c)). On the other hand, n-3 LC-PUFA stimulate fatty acid oxidation in the liver (via the activation of peroxisome proliferator activated receptor alpha (PPAR-alpha)). In patients with type 2 diabetes, fish oil dietary supplementation fails to reverse insulin resistance for unclear reasons, but systematically decreases plasma triglycerides. Conversely, in healthy humans, fish oil has many physiological effects. Indeed, fish oil reduces insulin response to oral glucose without altering the glycaemic response, abolishes exaggession at times of mental stress, decreases the activation of sympathetic activity during mental stress and also decreases plasma triglycerides. These effects are encouraging in the perspective of prevention of insulin resistance but further clinical and basic studies must be designed to confirm and complete our knowledge in this field.

Am J Physiol Regul Integr Comp Physiol. 2004 Mar;286(3):R519-27. Epub 2003 Nov 6.

Docosahexaenoic acid affects insulin deficiency- and insulin resistance-induced alterations in cardiac mitochondria.

Ovide-Bordeaux S, Grynberg A.

The effect of docosahexaenoic acid (DHA) intake on cardiac mitochondrial function was evaluated in permeabilized fibers in insulin deficiency and insulin resistance in rats. The insulin-deficient state was obtained by streptozotocin injection 2 mo before investigations. Insulin resistance was obtained by feeding a 62% fructose diet for 3 mo. DHA was incorporated in the diet to modify the fatty acid composition of cardiac membranes, including mitochondria. Insulin deficiency decreased mitochondrial creatine kinase (mi-CK) activity and mitochondrial sensitivity to ADP. DHA intake prevented these alterations. Moreover, the insulin-deficient state significantly decreased n-3 polyunsaturated fatty acids (PUFA) and slightly increased n-6 PUFA in both cardiac and mitochondrial membranes, inducing a significant increase in the n-6-to-n-3 ratio. DHA intake maintained high myocardial and mitochondrial DHA content. Insulin deficiency also decreased glutamate- and palmitoylcarnitine-supported mitochondrial respiration, but DHA intake did not prevent these effects. In contrast, insulin resistance did not affect mi-CK activity or sensitivity to ADP. However, insulin resistance influenced the myocardial fatty acid composition with decreased n-6 and n-3 PUFA contents and increased monounsaturated fatty acid content. Only slight alterations were observed in mitochondrial fatty acid composition, and they were corrected by DHA intake. Moreover, insulin resistance decreased the glutamate-supported respiration, and DHA intake did not influence this effect. In conclusion, the impairment of cardiac mitochondrial function was more pronounced in the insulin-deficient state than in insulin resistance. The modification of fatty acid composition of cardiac and mitochondrial membranes by DHA partially prevented the mitochondrial alterations induced in the two models.

Proc Nutr Soc. 2004 Feb;63(1):115-25.

Dietary PUFA and the metabolic syndrome in Indian Asians living in the UK.

Brady LM, Williams CM, Lovegrove JA.

Indian Asians living in the UK have a 50% higher CHD mortality rate compared with the indigenous Caucasian population, which cannot be attributed to traditional risk factors. Instead, features of the metabolic syndrome, including raised plasma triacylglycerol, reduced HDL-cholesterol (HDL-C) and an increased proportion of small dense LDL particles, together with insulin resistance and central obesity, are prevalent among this population. The present review examines evidence to support the hypothesis that an imbalance in dietary PUFA intake, specifically a higher intake of n-6 PUFA in combination with the lower intake of the long-chain (LC) n-3 PUFA, plays an important role in the prevalence of the metabolic syndrome observed in Indian Asians. Data are presented to illustrate the impact of manipulation of the background n-6 PUFA intake (moderate or high n-6 PUFA) and the subsequent response to supplementation with LC n-3 PUFA on blood lipids and insulin action in a group of Indian Asian volunteers. The results demonstrate that supplementation with LC n-3 PUFA had no impact on insulin action in those subjects consuming either the moderate- or high-n-6 PUFA diet. In the postprandial phase reductions in plasma triacylglycerol concentrations were greater in those consuming the high-n-6 PUFA background diet subsequent to fish oil supplementation. The present study concludes that, contrary to the central hypothesis, the prevalence of metabolic abnormalities in Indian Asians compared with Caucasians may not be attributable to differences in intakes of n-6 and n-3 PUFA.

Free Radic Biol Med. 2003 Oct 1;35(7):772-81.

Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and inflammatory markers in treated-hypertensive type 2 diabetic subjects.

Mori TA, Woodman RJ, Burke V, Puddey IB, Croft KD, Beilin LJ.

n-3 fatty acids reduce the risk of cardiovascular disease via a number of possible mechanisms. Despite this, there has been concern that these fatty acids may increase lipid peroxidation. The data in vivo are inconclusive, due in part to limitations in the methodologies. In this regard, the measurement of F2-isoprostanes provides a reliable assessment of in vivo lipid peroxidation and oxidant stress. This study aimed to assess the effects of supplementation with purified eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), the two major n-3 fatty acids, on urinary F2-isoprostanes and markers of inflammation, in type 2 diabetic patients. In a double-blind, placebo controlled trial of parallel design, 59 nonsmoking, treated-hypertensive, type 2 diabetic subjects, were randomized to 4 g daily of purified EPA, DHA, or olive oil for 6 weeks, while maintaining their usual diet. F2-isoprostanes, measured using gas chromatography-mass spectrometry in 24 h urines and C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), were measured before and after intervention. Thirty-nine men and 12 women aged 61.2 +/- 1.2 years, with body mass index (BMI), 29.5 +/- 0.5 kg/m²; 24 h blood pressure, 138/73 mmHg; HbA1c, 7.3 +/- 0.1% and fasting glucose, 7.9 +/- 0.2 mmol/l completed the intervention. Baseline urinary F2-isoprostanes were positively associated with HbA1c (p=.011) and fasting glucose (p=.032). Relative to the olive oil group, postintervention urinary F2-isoprostanes were decreased 19% by EPA (p=.017) and 20% by DHA (p=.014). There were no significant changes in CRP, IL-6, and TNF-alpha following EPA or DHA supplementation. In regression analysis, Delta F2-isoprostanes were

positively associated with Delta HbA1c ($p=.007$) independent of treatment group; and with Delta TNF-alpha ($p=.034$) independent of age, gender, BMI, and treatment group. There were no associations with Delta CRP or Delta IL-6. This study is the first report demonstrating that either EPA or DHA reduce in vivo oxidant stress without changing markers of inflammation, in treated hypertensive, type 2 diabetic subjects.

Proc Nutr Soc. 2003 May;62(2):447-53.

n-3 Polyunsaturated fatty acids, inflammation and obesity-related disease.

Browning LM.

Obese individuals are at increased risk from a range of metabolic diseases, including insulin resistance, dyslipidaemia and hypertension. Adipose tissue is an important endocrine organ, secreting a range of inflammatory mediators, including tumour necrosis factor alpha and interleukin 6. Circulating concentrations of these cytokines are increased in obesity and may contribute to the pathogenesis of metabolic diseases. The present review considers the evidence linking inflammation and obesity-related disease. The data show that an inflammatory phenotype, measured by serum sialic acid concentration, identifies individuals with insulin resistance, dyslipidaemia and hypertension. Serum sialic acid concentration increases progressively in obese individuals with none, one or multiple features of the metabolic syndrome, independent of BMI. Supplementation with long-chain n-3 polyunsaturated fatty acids has shown anti-inflammatory effects in studies of both healthy populations and in models of chronic inflammatory conditions. The effect on insulin sensitivity has been varied, with both positive and negative effects. This variability may relate to the metabolic characteristics of the study population; individuals with high background inflammation may derive greater benefits from n-3 polyunsaturated fatty acid supplements, suggesting a possible interaction between diet and phenotype. Future research is needed to fully evaluate the role of anti-inflammatory strategies in the dietary management of obesity.

Atherosclerosis. 2003 Jan;166(1):85-93.

Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients.

Woodman RJ, Mori TA, Burke V, Puddey IB, Barden A, Watts GF, Beilin LJ.

BACKGROUND: Type 2 diabetes and hypertension are both associated with an increased risk of atherothrombosis. We assessed whether purified eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil have differential effects on platelet, fibrinolytic and vascular function in patients with both conditions. **METHODS:** In a double-blind placebo-controlled trial of parallel design, 59 treated-hypertensive Type 2 diabetic men and postmenopausal women, were randomised to 4 g/day of EPA, DHA or olive oil (placebo) for 6 weeks. Collagen and PAF-stimulated platelet aggregation, collagen-stimulated thromboxane release (TXB2), plasma tPA and PAI-1 antigens, von Willebrand factor, p-selectin, and flow-mediated and glyceryl-trinitrate-mediated dilatation of the brachial artery, were examined before and at the end of intervention. **RESULTS:** Thirty-nine men and 12 women aged 61.2 \pm 1.2 year completed the study. Relative to placebo, DHA but not EPA supplementation significantly reduced collagen aggregation (16.9%, $P=0.05$) and TXB2 (18.8%, $P=0.03$). There were no significant changes in either PAF-stimulated platelet aggregation, fibrinolytic function or vascular function in either the EPA or DHA group relative to placebo. **CONCLUSION:** Highly purified DHA may be a more effective anti-thrombotic agent than EPA. However, longer-term studies assessing morbidity and mortality are needed in order to establish if DHA contributes to reducing CHD amongst Type 2 diabetic patients with treated hypertension.

J Assoc Physicians India. 2002 Aug;50:1028-33.

Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress--a prospective preliminary study.

Jain S, Gaiha M, Bhattacharjee J, Anuradha S.

BACKGROUND: A state of increased oxidative stress has been recognised in type 2 diabetes mellitus (DM). The present study was done to assess the effects of low dose omega-3 fatty acids substitution in patients with type 2 DM with special reference to oxidative stress. **METHOD:** Sixty-five patients with type 2 DM of body mass index (BMI) < 27 kg/m² and thirty age and sex matched healthy controls were evaluated for blood glucose, blood pressure and lipid profile and oxidative stress was assessed in them by measuring lipid peroxides (LP), diene conjugates (DC) and reduced glutathione (RG) in the serum. Of the 65, 40 motivated patients were randomly divided into two groups--group 1 comprising of fifteen patients prescribed a diabetic diet along with a placebo and group 2 consisting of twenty-five patients on the same diet with the addition of 0.6 g omega-3 fatty acids as one capsule Maxigard (containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) twice daily. All parameters were reassessed after six weeks. **RESULTS:** The levels of lipid peroxides (micromol/L), diene conjugates (OD units)

and reduced glutathione (mmol GSH/L) were significantly altered indicating increased oxidative stress in the diabetics compared to the healthy controls: 4.106 +/- 0.889, 2.751 +/- 0.424, 1.344 +/- 0.316 and 1.91 +/- 0.541, 1.735 +/- 0.315, 1.919 +/- 0.310, respectively ($p < 0.001$ for all the three). Patients in group 1 and 2 were comparable in all respects including oxidative stress at the start of therapy. After six weeks, on comparing the mean % changes in the three parameters of oxidative stress between the two groups, it was seen that the % change was significantly higher in group 2 (Maxigard group) compared to group 1 (Placebo; 5.22 +/- 1.056 ($p = 0.05$), 3.28 +/- 0.608 ($p = 0.01$), 5.27 +/- 0.585 ($p < 0.001$) and 0.82 +/- 0.123, 0.18 +/- 0.017, 0.56 +/- 0.035 ($p < 0.001$), respectively. The patients in group 2 also exhibited significantly greater improvement in glycemic status, blood pressure and lipid profiles. **CONCLUSIONS:** The present study documented the existence of a state of increased oxidative stress in type 2 diabetics. Significant beneficial effects of low dose omega-3 fatty acids substitution for PUFA-6 were observed not only on oxidative stress parameters but also on blood pressure and metabolic profile.

Am J Clin Nutr. 1999 Nov;70(5):817-25.

Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects.

Mori TA, Bao DQ, Burke V, Puddey IB, Watts GF, Beilin LJ.

BACKGROUND: Obesity in hypertensive patients is associated with dyslipidemia and insulin resistance, both of which are improved by weight control. n-3 Fatty acids have diverse effects on mechanisms underlying atherosclerosis, including a decrease in serum triacylglycerols and an increase in HDL(2) cholesterol. **OBJECTIVE:** The objective was to examine whether dietary fish enhances the effects of weight loss on serum lipids, glucose, and insulin in 69 overweight, treated hypertensive patients. **DESIGN:** Overweight patients being treated for hypertension were randomly assigned to either a daily fish meal (3.65 g n-3 fatty acids), a weight-loss regimen, the 2 regimens combined, or a control group for 16 wk. **RESULTS:** Sixty-three subjects completed the study. Weight decreased by a mean (+/-SEM) of 5.6 +/- 0.8 kg with energy restriction. Weight loss decreased fasting insulin ($P = 0.003$) and the area under the curve for insulin ($P = 0.003$) and glucose ($P = 0.047$) during an oral-glucose-tolerance test. The greatest decrease occurred in the fish + weight-loss group. There was no independent effect of fish on glucose or insulin. Fish increased HDL(2) cholesterol ($P = 0.004$) and decreased HDL(3) cholesterol ($P = 0.026$) without altering total, LDL, or HDL cholesterol. Weight loss had no effect on these variables. Fasting triacylglycerols fell significantly with fish consumption (29%) and weight loss (26%). The fish + weight-loss group showed the greatest improvement in lipids: triacylglycerols decreased by 38% ($P < 0.001$) and HDL(2) cholesterol increased by 24% ($P = 0.04$) compared with the control group. **CONCLUSIONS:** Incorporating a daily fish meal into a weight-loss regimen was more effective than either measure alone at improving glucose-insulin metabolism and dyslipidemia. Cardiovascular risk is likely to be substantially reduced in overweight hypertensive patients with a weight-loss program incorporating fish meals rich in n-3 fatty acids.

Atherosclerosis. 1998 Apr;137(2):419-27.

One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance: reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations.

Sirtori CR, Crepaldi G, Manzato E, Mancini M, Rivellesse A, Paoletti R, Pazzucconi F, Pamparana F, Stragliotto E.

n-3 Fatty acids in the form of ethyl esters (EE) allow lower daily doses and improved compliance. Administration of n-3 fatty acids to patients with glucose intolerance has led to controversial findings, some studies indicating worsening of the disorder, others no effect, or an improvement. A total of 935 patients with hypertriglyceridemia, associated with additional cardiovascular risk factors, i.e. glucose intolerance, NIDDM and/or arterial hypertension were entered a double blind (DB) protocol lasting 6 months with n-3 EE versus placebo, followed by a further 6 months of open study ($n = 868$) on 2 g a day of n-3 EE. At the end of the DB period, triglyceridemia in the total group was reduced significantly more by n-3 EE, without alterations in glycemic parameters. In the 6 months open follow up, patients on n-3 EE with type IIB hyperlipoproteinemia showed a significant reduction of total cholesterol, both in cases with (-4.15% vs. the 6 month levels) and without NIDDM (-3.8%). HDL-cholesterol had an overall mean rise of 7.4%, maximal in type IV patients with (+9.1%) and without (+10.1%) NIDDM. No alterations in glycemic parameters were detected in treated patients. Administration of n-3 EE to patients with hypertriglyceridemia associated with NIDDM or impaired glucose tolerance appears safe and effective.

Metabolism. 1997 Nov;46(11):1252-8.

Amelioration of insulin resistance and hypertension in a fructose-fed rat model with fish oil supplementation.

Huang YJ, Fang VS, Juan CC, Chou YC, Kwok CF, Ho LT.

In type II diabetic patients, one can detect several pathologic changes including insulin resistance and hypertension. Sprague-Dawley rats fed a fructose-rich diet (group F) exhibited these characteristic abnormalities within 2 weeks and were an excellent laboratory animal model for research on insulin action and development of hypertension. Since fish oils containing omega-3 fatty acids have a beneficial effect in preventing atherosclerotic diseases, we performed repeated experiments to test the effects of fish oil supplementation in group F rats. Compared with control rats on a normal diet (group C), group F consistently developed hypertriglyceridemia without elevated plasma free fatty acid (FFA), fasting hyperinsulinemia together with fasting hyperglycemia (insulin resistance syndrome), and systolic hypertension within 3 weeks. Insulin-stimulated glucose uptake and insulin binding of adipocytes were significantly reduced. Rats fed the same high-fructose diet but supplemented with fish oil (group O) had alleviation of all of these metabolic defects and a normalized insulin sensitivity and blood pressure. beta-Cell function as shown by plasma glucose and insulin responses to oral glucose remained intact in group F and group O. The plasma endothelin-1 (ET-1) level and ET-1 binding to adipocytes were not different among the three groups. Based on these results, we suggest that dietary high fructose induced hypertriglyceridemia and insulin resistance with normal islet function, and that the induced hypertension was not associated with plasma ET-1 abnormalities and was probably caused by other undefined pathologic changes that can be prevented by dietary omega-3 fatty acids.

Ann N Y Acad Sci. 1997 Sep 20;827:310-26.

Omega-3 and omega-6 fatty acids in the insulin resistance syndrome. Lipid and lipoprotein metabolism and atherosclerosis.

Rustan AC, Nenseter MS, Drevon CA.

Dietary fatty acids appear to be of significant importance for several of the most-common diseases in modern societies. To obtain more knowledge about the health consequences of dietary fatty acids, we depend upon a better understanding of the mechanisms of action of these fatty acids in vivo. With regard to the IRS, omega-3 PUFA may exert beneficial effects upon many of the associated pathophysiological metabolic changes. Omega-3 PUFA reduce fasting and postprandial TG, may improve insulin sensitivity (as shown in animal experiments), decrease platelet and leukocyte reactivity, alter immunological functions, and may slightly decrease blood pressure. Omega-3 PUFA may also beneficially influence vessel wall characteristics and blood rheology. Furthermore, both types of PUFA (omega-3 and omega-6) have been shown to inhibit cardiac arrhythmias in animals. The role of omega-3 PUFA in blood clotting and fibrinolysis still remains controversial, whereas omega-6 fatty acids may lead to increased oxidation of lipoproteins. Regardless of the effects on LDL oxidizability, both types of PUFA have shown beneficial effects on the development of atherosclerosis. As yet, little is known about the effect of specific omega-6 fatty acids with respect to the IRS. Potential adverse effects of dietary PUFA must not be neglected, but should be viewed in light of the beneficial effects of these agents.

Am J Clin Nutr. 1997 Jun;65(6):1874-81.

N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study.

Sirtori CR, Paoletti R, Mancini M, Crepaldi G, Manzato E, Rivellese A, Pamparana F, Stragliotto E.

A multicenter, randomized, double-blind, placebo-controlled study evaluated the possible worsening of glycemic control after a moderate daily intake of n-3 fatty acid ethyl esters in patients with hypertriglyceridemia with and without glucose intolerance or diabetes. A total of 935 patients of both sexes in 63 Italian clinical centers were selected; 55% had either impaired glucose tolerance or non-insulin-dependent diabetes mellitus (NIDDM). They received for 2 mo either 1 g n-3 ethyl esters three times a day or a corresponding placebo, followed by 4 mo of either 1 g n-3 ethyl esters twice a day or placebo. In addition to the complete lipid and lipoprotein evaluation, patients with impaired glucose tolerance also underwent an oral-glucose-tolerance test; in patients with NIDDM, serum insulin and glycated hemoglobin (Hb A1c) concentrations were determined. Plasma triacylglycerol concentrations decreased significantly, up to 21.53% at 6 mo compared with baseline (decreased 15% compared with placebo), with a tendency toward a progressive reduction with time. There was no evidence for a different response in patients with either NIDDM or impaired glucose tolerance. Among NIDDM patients, the triacylglycerol reduction was greater in those with high-density-lipoprotein cholesterol \leq 0.91 mmol/L. There was no alteration in the major glycemic indexes: fasting glucose, Hb A1c, insulinemia, and oral glucose tolerance in patients with impaired glucose tolerance or NIDDM after treatment with n-3 ethyl esters. Treatment with a moderate daily dose of n-3 ethyl esters over a prolonged period of time significantly reduced triacylglycerol concentrations without any worsening of glucose tolerance in patients with hypertriglyceridemia with and without impaired glycemic regulation.

Diabetes Care. 1996 Nov;19(11):1207-13.

Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia.

Rivellese AA, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Mancini M, Riccardi G.

OBJECTIVE: The aim of this study was to evaluate the long-term (6-month) effects of moderate fish oil supplementation on insulin sensitivity and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. **RESEARCH DESIGN AND METHODS:** The study has been performed according to a randomized double-blind placebo-controlled design with a parallel group sequence. After a washout period of 4 weeks and a run-in period of 3 weeks, 16 NIDDM patients with hypertriglyceridemia (triglyceride [TG], 2.25-5.65 mmol/l) were randomly assigned to either fish oil (2.7 g/day eicosapentaenoic plus docosahexaenoic acid for 2 months, then 1.7 g/day for 4 more months) (n = 8) or placebo (n = 8). Diet and hypoglycemic drugs remained unchanged throughout the whole experiment. At baseline and after 6 months, insulin sensitivity was measured by euglycemic hyperinsulinemic clamp (insulin infused, 2.0 mIU.kg⁻¹ body wt.min⁻¹). At the same time, blood glucose control, fasting and postprandial serum insulin and nonesterified fatty acid (NEFA) concentrations, and fasting plasma lipoprotein concentrations were evaluated. **RESULTS:** In the group treated with fish oil compared with the baseline, there was: 1) a significant reduction in both plasma TG (2.92 +/- 0.23 vs. 3.85 +/- 0.32 [mean +/- SE] mmol/l, P < 0.001) and VLDL-TG (2.35 +/- 0.24 vs. 4.25 +/- 0.66 mmol/l, P < 0.01), without significant changes in blood glucose control; 2) a significant reduction in fasting NEFA concentrations (572 +/- 100 vs. 825 +/- 131 μmol/l, P < 0.01); and 3) a significant enrichment in long-chain omega-3 fatty acids of erythrocyte membrane phospholipids. In the placebo group, there were no changes in any of the variables analyzed. The insulin-mediated glucose uptake was unchanged in both groups (fish oil, 4.04 +/- 0.82 mg.kg⁻¹.min⁻¹ at baseline and 3.96 +/- 0.50 mg.kg⁻¹.min⁻¹ at 6 months; placebo, 3.51 +/- 0.62 mg.kg⁻¹.min⁻¹ at baseline and 4.09 +/- 0.49 mg.kg⁻¹.min⁻¹ at 6 months). **CONCLUSIONS:** In NIDDM patients with hypertriglyceridemia, moderate amounts of fish oil induce a long-term significant reduction in plasma triglycerides, VLDL triglycerides, and NEFA and a significant enrichment in the erythrocyte phospholipid content of long-chain omega-3 fatty acids, without deteriorating blood glucose control. However, this amount of omega-3 fatty acids was unable to improve insulin sensitivity in this group of patients.

J Nutr. 1996 Aug;126(8):1951-8.

Dietary (n-3) polyunsaturated fatty acids improve adipocyte insulin action and glucose metabolism in insulin-resistant rats: relation to membrane fatty acids.

Luo J, Rizkalla SW, Boillot J, Alamowitch C, Chaib H, Bruzzo F, Desplanque N, Dalix AM, Durand G, Slama G.

To study the effects of dietary fish oil on insulin-stimulated glucose metabolism in adipocytes of insulin-resistant rats (rats fed 50% sucrose and 30% fat), eighteen 5-wk-old Sprague-Dawley rats were fed, for 6 wk, a diet containing 30% fat as either fish oil (FO) or a mixture of vegetable and animal oils [control oils (CO)]. A third reference group was fed a standard diet (62% corn starch and 13% fat). At the end of the 6-wk period, the two experimental groups had comparable plasma glucose concentrations that were higher than that found in the reference group. FO feeding corrected the hyperinsulinemia of the experimental rats (P < 0.05) to reach values in the reference group. Plasma triacylglycerol (P < 0.01) and cholesterol (P < 0.001) concentrations were also lower in rats fed FO than in those fed CO. The body weights of FO-fed rats were similar to that of CO-fed rats, but epididymal adipose tissue weight was lower (P < 0.01). Adipocytes of FO-fed rats, compared with those of CO-fed rats, had high insulin-stimulated glucose transport (P < 0.05), oxidation (P < 0.001) and incorporation into total lipids (P < 0.05). The incorporation of (n-3) polyunsaturated fatty acids in adipocyte membrane phospholipids was higher in FO-fed rats than in those fed CO (P < 0.0001). Insulin action was positively correlated with the fatty acid unsaturation index in membrane phospholipids. Thus dietary fish oil has beneficial effects on insulinemia, plasma lipids and insulin-stimulated glucose metabolism in insulin-resistant slightly diabetic rats.

Ann Intern Med. 1995 Dec 15;123(12):911-8.

Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial.

Toft I, Bonna KH, Ingebretsen OC, Nordoy A, Jenssen T.

OBJECTIVE: To determine whether dietary supplementation with fish oil adversely affects glycemic control in patients with hypertension. **DESIGN:** Randomized, double-blind, placebo-controlled study. **PATIENTS:** 78 persons with untreated hypertension recruited from a population survey. **INTERVENTION:** Participants were randomly assigned to receive eicosapentaenoic and docosahexaenoic acids, 4 g/d, or corn oil placebo, 4 g/d, for 16 weeks. **MEASUREMENTS:** An oral glucose tolerance test; assessments of insulin release, glucose disposal, and insulin sensitivity done using the hyperglycemic clamp technique to keep plasma glucose levels at 10 mmol/L for 180 minutes; assessment of insulin sensitivity done using a euglycemic hyperinsulinemic clamp technique (infusing insulin and glucose to keep plasma glucose levels at 5 mmol/L); assessments of lipid levels and blood pressure. Measurements were done before and after intervention. **RESULTS:** Changes in integrated glucose and insulin response after the oral glucose challenge did not differ between the fish oil and corn oil groups after intervention (-0.6 +/- 0.7

compared with -1.0 ± 0.6 mmol/L [$P > 0.3$] for integrated glucose and 143 ± 76 compared with 169 ± 84 pmol/L [$P > 0.3$] for insulin response). Changes in first-phase insulin release (34 ± 72 pmol/L in the fish oil group compared with 191 ± 112 pmol/L in the corn oil group [$P > 0.3$]), second-phase insulin release (179 ± 66 pmol/L compared with 257 ± 122 pmol/L [$P > 0.3$]), and insulin sensitivity index (-0.03 ± 0.01 compared with -0.01 ± 0.01 [$\mu\text{mol/kg}\cdot\text{min}$ divided by pmol/L]; $P > 0.3$) were also similar in both groups after treatment. Fish oil lowered systolic blood pressure by 3.8 mm Hg more than control ($P = 0.04$) and lowered diastolic blood pressure by 2.0 mm Hg more than control ($P = 0.10$). After fish oil treatment, triglyceride levels decreased by 0.28 ± 0.08 mmol/L more than control ($P = 0.01$), and very-low-density lipoprotein cholesterol levels decreased by 0.13 ± 0.04 mmol/L more than control ($P = 0.01$). CONCLUSION: Fish oil, in doses that reduce blood pressure and lipid levels in hypertensive persons, does not adversely affect glucose metabolism.

Diabetes Care. 1994 Jan;17(1):37-44.

Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study.

Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D.

OBJECTIVE--To study the effects of a low dose of omega-3 fatty acids on platelet function and other cardiovascular risk factors in patients with non-insulin-dependent diabetes mellitus (NIDDM). **RESEARCH DESIGN AND METHODS**--We performed a randomized, prospective, double-blind, controlled study of a low dose of omega-3 fatty acids (2.5 g/day) in 20 ambulatory subjects with NIDDM. Subjects ingested five 1-g fish oil capsules each containing 0.5 g omega-3 fatty acids or five 1-g safflower oil capsules per day for 6 weeks followed by a 6-week washout period. **RESULTS**--Nine subjects completed the study in each group. Both groups exhibited moderate control of glucose levels; modest elevations in baseline total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels; and normal blood pressure values. In the fish oil group, plasma omega-3 fatty acid levels increased significantly. Fish oil significantly reduced the slope of the dose-response curves for collagen-induced platelet aggregation to one-third the value observed with safflower oil. No difference was observed in collagen-induced production of thromboxane A2 (TXA2, measured as the stable derivative TXB2), or in adenosine-5'-diphosphate (ADP) induced platelet aggregation or TXA2 generation. Patients with high initial collagen-induced platelet TXA2 production showed a significantly larger drop after fish oil than safflower oil. Fish oil significantly reduced TG levels by 44 mg/dl and decreased upright systolic blood pressure (sBP) by 8 mmHg compared with safflower oil. Fish oil caused a significant but small increase in HbA1c (0.56%) and total cholesterol (20 mg/dl) but had no effect on fasting glucose, high-density lipoprotein cholesterol, or LDL-cholesterol levels. **CONCLUSIONS**--Small doses of fish oil inhibit platelet aggregation and TXA2 production, reduce upright sBP and TG levels, and have only a small effect on glucose and cholesterol levels in patients with moderately controlled NIDDM. Small quantities of omega-3 fatty acids or dietary fish are safe and potentially beneficial in NIDDM patients.

Diabetes Care. 1993 May;16(5):683-8.

Effects of low-dose EPA-E on glycemic control, lipid profile, lipoprotein(a), platelet aggregation, viscosity, and platelet and vessel wall interaction in NIDDM.

Westerveld HT, de Graaf JC, van Breugel HH, Akkerman JW, Sixma JJ, Erkelens DW, Banga JD.

OBJECTIVE--To assess the effects of low-dose eicosapentaenoic acid-ethyl-ester on diabetes regulation, lipid metabolism, blood rheology, and platelet reactivity. **RESEARCH DESIGN AND METHODS**--In a double-blind, randomized, placebo-controlled study, 24 NIDDM subjects received 1800 mg of EPA-E, 900 mg of EPA-E, or a placebo (1656 mg olive oil) daily for 8 wk. **RESULTS**--The EPA:arachidonic acid plasma ratio increased over an 8-wk period, then declined after a 4-wk wash-out period in the fish-oil groups in a dose-dependent way. Platelet-activating factor-induced platelet aggregation decreased from $75 \pm 7\%$ at wk 0 to $35 \pm 21\%$ at wk 8 in the 900-mg group ($P = 0.016$) and from 72 ± 11 to $40 \pm 30\%$ in the 1800-mg group ($P = 0.039$), but did not change in the placebo group. No effects on ADP- or collagen-induced aggregation could be attributed to EPA-E. In the 1800-mg group low-density-lipoprotein cholesterol increased significantly, without concomitant rise in apolipoprotein B. Triglycerides, glycemic control, lipoprotein (a), blood and plasma viscosity, erythrocyte deformability, and platelet adhesion to and aggregate formation on extracellular endothelial cell matrix were not significantly influenced. **CONCLUSIONS**--Purified EPA-E in doses of 900 and 1800 mg reduces Platelet-activating factor-induced platelet aggregation without negatively affecting glycemic control. Low-density-lipoprotein cholesterol was elevated in the 1800-mg group.

Atherosclerosis. 1991 Mar;87(1):65-73.

A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients.

Annuzzi G, Rivellese A, Capaldo B, Di Marino L, Iovine C, Marotta G, Riccardi G.

Eight male non-insulin-dependent diabetic patients participated in a double-blind randomized cross-over study (2 weeks for each period) evaluating the effects of 10 g/day fish oil dietary supplementation on glucose and lipid metabolism. Fasting serum triglyceride concentrations were decreased by fish oil because of a reduction in VLDL (1.4 +/- 0.2 vs. 1.9 +/- 0.2 mmol/l, P less than 0.025). LDL cholesterol concentration was instead increased (3.4 +/- 0.3 vs. 2.8 +/- 0.3 mmol/l, P less than 0.025) and net changes in VLDL triglyceride and in LDL cholesterol were inversely correlated ($r = -0.86$, P less than 0.01). Plasma free fatty acids concentrations and turnover rate [(3H]palmitate method) were similar after fish oil and placebo. Fish oil supplement did not induce significant changes in fasting blood glucose (8.1 +/- 1.1 vs. 8.5 +/- 1.2 mmol/l) and average daily blood glucose (BG) (9.4 +/- 3.2 vs. 9.3 +/- 3.5 mmol/l). Glucose stimulated plasma insulin response during a hyperglycemic clamp was not significantly influenced by fish oil both in the early phase and during steady state. Insulin sensitivity (M/I index) was also unchanged. In conclusion, this study shows that a dietary supplement of fish oil decreases plasma triglyceride levels in non-insulin-dependent diabetic patients, an increased conversion rate of VLDL to LDL playing a role in this change. With this dosage of fish oil no relevant variations in glycemic control, insulin secretion and insulin sensitivity occurred.

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