

## ABSTRACTS

### Heart disease

#### **A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group.**

**BACKGROUND:** It is known that obesity, sodium intake, and alcohol consumption factors influence blood pressure. In this clinical trial, Dietary Approaches to Stop Hypertension, we assessed the effects of dietary patterns on blood pressure. **METHODS:** We enrolled 459 adults with systolic blood pressures of less than 160 mm Hg and diastolic blood pressures of 80 to 95 mm Hg. For three weeks, the subjects were fed a control diet that was low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States. They were then randomly assigned to receive for eight weeks the control diet, a diet rich in fruits and vegetables, or a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels. **RESULTS:** At base line, the mean (+/-SD) systolic and diastolic blood pressures were 131.3+/-10.8 mm Hg and 84.7+/-4.7 mm Hg, respectively. The combination diet reduced systolic and diastolic blood pressure by 5.5 and 3.0 mm Hg more, respectively, than the control diet ( $P<0.001$  for each); the fruits-and-vegetables diet reduced systolic blood pressure by 2.8 mm Hg more ( $P<0.001$ ) and diastolic blood pressure by 1.1 mm Hg more than the control diet ( $P=0.07$ ). Among the 133 subjects with hypertension (systolic pressure,  $> \text{ or } =140$  mm Hg; diastolic pressure,  $> \text{ or } =90$  mm Hg; or both), the combination diet reduced systolic and diastolic blood pressure by 11.4 and 5.5 mm Hg more, respectively, than the control diet ( $P<0.001$  for each); among the 326 subjects without hypertension, the corresponding reductions were 3.5 mm Hg ( $P<0.001$ ) and 2.1 mm Hg ( $P=0.003$ ). **CONCLUSIONS:** A diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat can substantially lower blood pressure. This diet offers an additional nutritional approach to preventing and treating hypertension.

*N Engl J Med. 1997 Apr 17;336(16):1117-24*

#### **Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group.**

**BACKGROUND:** The effect of dietary composition on blood pressure is a subject of public health importance. We studied the effect of different levels of dietary sodium, in conjunction with the Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in vegetables, fruits, and low-fat dairy products, in persons with and in those without hypertension. **METHODS:** A total of 412 participants were randomly assigned to eat either a control diet typical of intake in the United States or the DASH diet. Within the assigned diet, participants ate foods with high, intermediate, and low levels of sodium for 30 consecutive days each, in random order. **RESULTS:** Reducing the sodium intake from the high to the intermediate level reduced the systolic blood pressure by 2.1 mm Hg ( $P<0.001$ ) during the control diet and by 1.3 mm Hg ( $P=0.03$ ) during the DASH diet. Reducing the sodium intake from the intermediate to the low level caused additional reductions of 4.6 mm Hg during the control diet ( $P<0.001$ ) and 1.7 mm Hg during the DASH diet ( $P<0.01$ ). The effects of sodium were observed in participants with and in those without hypertension, blacks and those of other races, and women and men. The DASH diet was associated with a significantly lower systolic blood pressure at each sodium level; and the difference was greater with high sodium levels than with low ones. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mm Hg lower in participants without hypertension, and 11.5 mm Hg lower in participants with hypertension. **CONCLUSIONS:** The reduction of sodium intake to levels below the current recommendation of 100 mmol per day and the DASH diet both lower blood pressure substantially, with greater effects in combination than singly. Long-term health benefits will depend on the ability of people to make long-lasting dietary changes and the increased availability of lower-sodium foods.

*N Engl J Med. 2001 Jan 4;344(1):3-10.*

#### **Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial.**

**BACKGROUND:** Effects of diet on blood lipids are best known in white men, and effects of type of carbohydrate on triacylglycerol concentrations are not well defined. **OBJECTIVE:** Our goal was to determine the effects of diet on plasma lipids, focusing on subgroups by sex, race, and baseline lipid concentrations. **DESIGN:** This was a randomized controlled outpatient feeding trial conducted in 4 field centers. The subjects were 436 participants of the Dietary Approaches to Stop Hypertension (DASH) Trial [mean age: 44.6 y; 60% African American; baseline total cholesterol:  $< \text{ or } = 6.7$  mmol/L ( $< \text{ or } = 260$  mg/dL)]. The intervention consisted of eight week of a control diet, a diet increased in fruit and vegetables, or a diet increased in fruit, vegetables, and low-fat dairy products and reduced in saturated fat, total fat, and cholesterol (DASH diet), during which time subjects remained weight stable. The main outcome measures were fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol. **RESULTS:** Relative to the control diet, the DASH diet resulted in lower total (-0.35 mmol/L, or -13.7 mg/dL), LDL (-0.28 mmol/L,

or -10.7 mg/dL), and HDL- (-0.09 mmol/L, or -3.7 mg/dL) cholesterol concentrations (all  $P < 0.0001$ ), without significant effects on triacylglycerol. The net reductions in total and LDL cholesterol in men were greater than those in women by 0.27 mmol/L, or 10.3 mg/dL ( $P = 0.052$ ), and by 0.29 mmol/L, or 11.2 mg/dL ( $P < 0.02$ ), respectively. Changes in lipids did not differ significantly by race or baseline lipid concentrations, except for HDL, which decreased more in participants with higher baseline HDL-cholesterol concentrations than in those with lower baseline HDL-cholesterol concentrations. The fruit and vegetable diet produced few significant lipid changes. **CONCLUSIONS:** The DASH diet is likely to reduce coronary heart disease risk. The possible opposing effect on coronary heart disease risk of HDL reduction needs further study.

*Am J Clin Nutr.* 2001 Jul;74(1):80-9

### **Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study.**

**BACKGROUND:** Few studies have examined associations of fish consumption with ischemic heart disease (IHD) risk among older adults or how different types of fish meals relate to IHD risk. **METHODS AND RESULTS:** In a population-based prospective cohort study, usual fish consumption was ascertained at baseline among 3910 adults aged  $>$  or  $=65$  years and free of known cardiovascular disease in 1989 and 1990. Consumption of tuna and other broiled or baked fish correlated with plasma phospholipid long-chain n-3 fatty acids, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. Over 9.3 years' mean follow-up, there were 247 IHD deaths (including 148 arrhythmic deaths) and 363 incident nonfatal myocardial infarctions (MIs). After adjustment for potential confounders, consumption of tuna or other broiled or baked fish was associated with lower risk of total IHD death ( $P$  for trend=0.001) and arrhythmic IHD death ( $P=0.001$ ) but not nonfatal MI ( $P=0.44$ ), with 49% lower risk of total IHD death and 58% lower risk of arrhythmic IHD death among persons consuming tuna/other fish three or more times per week compared with less than once per month. In similar analyses, fried fish/fish sandwich consumption was not associated with lower risk of total IHD death, arrhythmic IHD death, or nonfatal MI but rather with trends toward higher risk. **CONCLUSIONS:** Among adults aged  $>$  or  $=65$  years, modest consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, is associated with lower risk of IHD death, especially arrhythmic IHD death. Cardiac benefits of fish consumption may vary depending on the type of fish meal consumed.

*Circulation.* 2003 Mar 18;107(10):1372-7

### **C-reactive protein and coronary artery disease.**

Evidence suggests that inflammation plays a key role in the pathogenesis of atherosclerosis. The chronic inflammatory process can develop to an acute clinical event by the induction of plaque rupture and therefore cause acute coronary syndromes. The aim of this study was to determine the serum levels of the circulating acute-phase reactant C-reactive protein (CRP), which is a sensitive indicator of inflammation, in patients with chronic stable coronary artery disease (CAD) and acute coronary syndromes (ACS). We studied 56 subjects: 1) 25 consecutive patients (18 men, seven women; mean age, 68.5  $\pm$  14.3 years, range, 40-86) with unstable angina (UA) or acute myocardial infarction (AMI); 2) 31 consecutive patients (25 men, six women; mean age 64  $\pm$  12.7; range, 47-83, years) with signs and symptoms of clinically stable CAD. High-sensitivity-C-reactive protein (hs-CRP) levels were determined with a commercially available enzyme-linked immunoassay method. In patients with unstable angina and AMI before reperfusion therapy, CRP levels were not significantly different to those in patients with stable CAD (5.96  $\pm$  2.26 versus 4.35  $\pm$  2.6 mg/L;  $P = 0.12$ ), but tended to be higher in patients with unstable angina and AMI. Baseline CRP levels in the subgroup of patients with AMI (6.49  $\pm$  2.28 mg/L) were significantly higher than levels in patients with stable CAD (4.35  $\pm$  2.6 mg/L;  $P = 0.02$ ). CRP levels in patients with unstable angina and AMI were measured four times during a 72-hour period (0, 12, 24, and 72 hours). The lowest value was observed at baseline and differed significantly from values measured at any other time of the observation period ( $P < 0.001$ ; 5.96  $\pm$  2.26; 9.5  $\pm$  9.04, 18.25  $\pm$  11.02; 20.25  $\pm$  10.61). CRP levels after 12, 24, and 72 hours were also significantly different to the initial values for patients with stable CAD ( $P < 0.01$ ). There was no correlation between CRP and creatine kinase (CK), CK-MB isoenzyme, or troponin I positivity as markers for the extent of the myocardial injury during the observation period. Baseline levels of serum CRP tended to be higher in patients with unstable angina or AMI but were not significantly different from levels in patients with chronic stable CAD. In the subgroup of patients with AMI, baseline CRP levels were significantly higher than the levels in patients with stable CAD. CRP as a marker of inflammation is significantly increased in patients with AMI and unstable angina shortly after the onset of symptoms (after a period of 12 hours), supporting the hypothesis of an activation of inflammatory mechanisms in patients with an acute coronary syndrome or AMI.

*Jpn Heart J.* 2002 Nov;43(6):607-19

## **Silymarin**

### **Effect of the flavanolignans of Silybum marianum L. on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes.**

The effect of several flavanolignans (silicristin, silidianin, silybin and isosilybin) present in silymarin, the extract of Silybum marianum fruits, was tested on lipid peroxidation in rat liver microsomes and freshly isolated hepatocytes. In microsomes lipid peroxidation was generated by ADP/Fe<sup>2+</sup> and NADPH. All flavanolignans inhibited peroxidation in a concentration dependent manner. In hepatocytes lipid peroxidation was induced by ADP/Fe<sup>3+</sup> complex and cell damage was evaluated as LDH activity

released in the medium. The inhibition of the peroxidative process by flavanolinans was also evident in this model, even if with a potency order different from that found in microsomes. In contrast, the effect on LDH release was significant only for silybin and isosilybin, the other compounds being inactive on this parameter.

*Pharmacol Res. 1992 Feb-Mar;25(2):147-54*

### **The effects of silymarin on experimental phalloidine poisoning.**

The hepatoprotective action of silymarin, the active principle extracted from the fruit of *Silybum marianum* (L.) Gaertn., in animals (dogs, rabbits, rats, mice) intoxicated with phalloidine is evident, both after protective and curative treatment. A dose of 15 mg/kg of silymarin protects every animal when given 60 minutes before the toxin. When injected 10 minutes after phalloidine, a dose of 100 mg/kg of silymarin again provides total protection. However, as the time span between administration of the toxic substance and start of treatment increases, so the efficacy of silymarin decreases; after 30 minutes its curative effect is negligible. The histochemical and histoenzymological studies show that during intoxication of the mice by phalloidine, silymarin inhibits the effect of the toxic substance and regulates the functions of the hepatocyte, when given either 60 minutes before or 10 minutes after phalloidine.

*Arzneimittelforschung. 1975 Jan;25(1):89-96*

### **Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat.**

Silymarin, a flavonoid extracted from the seeds of the milk thistle, *Silybum marianum*, increases the redox state and the total glutathione content of the liver, intestine, and stomach of the rat. The same treatment does not affect the levels of the tripeptides in the kidney, lung and spleen. This selective effect of the flavonoid on the digestive organs is ascribed to its pharmacokinetics on the digestive track, where the biliary concentration of silymarin is increased and maintained via the entero-hepatic circulation.

*Planta Med. 1989 Oct;55(5):420-2*

### **Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells.**

The effects of the flavonoid silibinin, which is used for the treatment of liver diseases, on the formation of reactive oxygen species and eicosanoids by human platelets, white blood and endothelial cells were studied. Silibinin proved to be a strong scavenger of HOCl (IC<sub>50</sub> 7 microM), but not of O<sub>2</sub><sup>-</sup> (IC<sub>50</sub> > 200 microM) produced by human granulocytes. The formation of leukotrienes via the 5-lipoxygenase pathway was strongly inhibited. In human granulocytes IC<sub>50</sub>-values of 15 microM and 14.5 microM silibinin were detected for LTB<sub>4</sub> and LTC<sub>4</sub>/D<sub>4</sub>/E<sub>4</sub>/F<sub>4</sub> formation, respectively. In contrast to this, three- to fourfold silibinin concentrations were necessary to half maximally inhibit the cyclooxygenase pathway. For PGE<sub>2</sub> formation by human monocytes an IC<sub>50</sub>-value of 45 microM silibinin was found. IC<sub>50</sub>-values of 69 microM and 52 microM silibinin were determined for the inhibition of TXB<sub>2</sub> formation by human thrombocytes and of 6-K-PGF<sub>1</sub> alpha formation by human omentum endothelial cells, respectively. Thus, the deleterious effects of HOCl that can lead to cell death, and those of leukotrienes that are especially important in inflammatory reactions, can be inhibited by silibinin in concentrations that are reached in vivo after the usual clinical dose. Silibinin is thought not only to display hepatoprotective properties but might also be cytoprotective in other organs and tissues.

*Life Sci. 1996;58(18):1591-600*

### **Scavenging of reactive oxygen species by silibinin dihemisuccinate.**

Silibinin dihemisuccinate (SDH) is a flavonoid of plant origin with hepatoprotective effects which have been partially attributed to its ability to scavenge oxygen free radicals. In the present paper the antioxidant properties of SDH were evaluated by studying the ability of this drug to react with relevant biological oxidants such as superoxide anion radical (O<sub>2</sub><sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl radical (HO $\cdot$ ) and hypochlorous acid (HOCl). In addition, its effect on lipid peroxidation was investigated. SDH is not a good scavenger of O<sub>2</sub><sup>-</sup> and no reaction with H<sub>2</sub>O<sub>2</sub> was detected within the sensitivity limit of our assay. However, it reacts rapidly with HO $\cdot$  radicals in free solution at approximately diffusion-controlled rate ( $K = (1.0-1.2) \times 10^{10}$  M/sec) and appears to be a weak iron ion chelator. SDH at concentrations in the micromolar range protected alpha 1-antiproteinase against inactivation by HOCl, showing that it is a potent scavenger of this oxidizing species. Luminol-dependent chemiluminescence induced by HOCl was also inhibited by SDH. The reaction of SDH with HOCl was monitored by the modification of the UV-visible spectrum of SDH. The studies on rat liver microsome lipid peroxidation induced by Fe(III)/ascorbate showed that SDH has an inhibitory effect, which is dependent on its concentration and the magnitude of lipid peroxidation. This work supports the reactive oxygen species scavenger action ascribed to SDH.

*Biochem Pharmacol. 1994 Aug 17;48(4):753-9*

### **The effect of silibinin (Legalon) on the the free radical scavenger mechanisms of human erythrocytes in vitro.**

The effect of Legalon was investigated parallel with that of Adriblastina (doxorubicin) and paracetamol on some parameters characterizing the free radical scavenger mechanisms of human erythrocytes in vitro and on the time of acid hemolysis performed

in aggregometer. Observations suggest that Adriablastina enhances the lipid peroxidation of the membrane of red blood cells, while paracetamol causes significant depletion of intracellular glutathione level, thus decreasing the free radical eliminating capacity of the glutathione peroxidase system. Legalon on the other hand, is able to increase the activity of both superoxide dismutase and glutathione peroxidase, which may explain the protective effect of the drug against free radicals and also the stabilizing effect on the red blood cell membrane, shown by the increase of the time of full haemolysis.

*Acta Physiol Hung. 1992;80(1-4):375-80*

### **Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin.**

The flavonoid silibinin, the main compound extracted from the milk thistle *Silybum marianum*, displays hepatoprotective properties in acute and chronic liver injury. To further elucidate the mechanisms by which it acts, we studied the effects of silibinin on different functions of isolated rat Kupffer cells, namely the formation of superoxide anion radical (O<sub>2</sub><sup>-</sup>), nitric oxide (NO), tumor necrosis factor alpha (TNF-alpha), prostaglandin E(2) (PGE(2)), and leukotriene B(4) (LTB(4)). Production of O<sub>2</sub><sup>-</sup> and NO were inhibited in a dose-dependent manner, with an 50 percent inhibitory concentration (IC(50)) value around 80 micro mol/L. No effect on TNF-alpha formation was detected. Opposite effects were found on the cyclooxygenase and 5-lipoxygenase pathway of arachidonic acid metabolism. Whereas no influence on PGE(2) formation was observed with silibinin concentrations up to 100 micro mol/L, a strong inhibitory effect on LTB(4) formation became evident. The IC(50)-value for inhibiting the formation of this eicosanoid was determined to be 15 micro mol/L silibinin. The strong inhibition of LTB(4) formation by silibinin was confirmed in experiments with phagocytic cells isolated from human liver. Hence, while rather high concentrations of silibinin are necessary to diminish free radical formation by activated Kupffer cells, significant inhibition of the 5-lipoxygenase pathway already occurs at silibinin concentrations which are achieved in vivo. Selective inhibition of leukotriene formation by Kupffer cells can at least partly account for the hepatoprotective properties of silibinin.

*Hepatology. 1996 Apr;23(4):749-54*

### **Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients.**

**BACKGROUND/AIMS:** Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals. The aim of this study was to ascertain whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis. **METHODS:** A 12-month open, controlled study was conducted in two well-matched groups of insulin-treated diabetics with alcoholic cirrhosis. One group (n=30) received 600 mg silymarin per day plus standard therapy, while the control group (n=30) received standard therapy alone. The efficacy parameters, measured regularly during the study, included fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria levels, glycosylated hemoglobin (HbA1c) and malondialdehyde levels. **RESULTS:** There was a significant decrease (p<0.01) in fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria and HbA1c levels already after four months of treatment in the silymarin group. In addition, there was a significant decrease (p<0.01) in fasting insulin levels and mean exogenous insulin requirements in the treated group, while the untreated group showed a significant increase (p<0.05) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease (p<0.01) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. Another interesting finding was the significant decrease (p<0.01) in malondialdehyde/levels observed in the treated group. **CONCLUSIONS:** These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

*J Hepatol. 1997 Apr;26(4):871-9*

### **Silibinin decreases prostate-specific antigen with cell growth inhibition via G1 arrest, leading to differentiation of prostate carcinoma cells: implications for prostate cancer intervention.**

Reduction in serum prostate-specific antigen (PSA) levels has been proposed as an endpoint biomarker for hormone-refractory human prostate cancer intervention. We examined whether a flavonoid antioxidant silibinin (an active constituent of milk thistle) decreases PSA levels in hormone-refractory human prostate carcinoma LNCaP cells and whether this effect has biological relevance. Silibinin treatment of cells grown in serum resulted in a significant decrease in both intracellular and secreted forms of PSA concomitant with a highly significant to complete inhibition of cell growth via a G1 arrest in cell cycle progression. Treatment of cells grown in charcoal-stripped serum and 5alpha-dihydrotestosterone showed that the observed effects of silibinin are those involving androgen-stimulated PSA expression and cell growth. Silibinin-induced G1 arrest was associated with a marked decrease in the kinase activity of cyclin-dependent kinases (CDKs) and associated cyclins because of a highly significant decrease in cyclin D1, CDK4, and CDK6 levels and an induction of Cip1/p21 and Kip1/p27 followed by their increased binding with CDK2. Silibinin treatment of cells did not result in apoptosis and changes in p53 and bcl2, suggesting that the observed increase in Cip1/p21 is a p53-independent effect that does not lead to an apoptotic cell death pathway. Conversely, silibinin treatment resulted in a significant neuroendocrine differentiation of LNCaP cells as an alternative pathway after Cip1/p21 induction and G1 arrest. Together, these results suggest that silibinin could be a useful agent for the intervention of hormone-refractory human prostate cancer.



## ABSTRACTS

### Omega - 3 fatty acids

#### **Omega-3 fatty acid supplementation increases anti-inflammatory cytokines and attenuates systemic disease sequelae in experimental pancreatitis.**

**BACKGROUND:** The cytokines involved in the systemic inflammatory response in acute pancreatitis (AP) comprise lipid mediators (eg, prostanooids, thromboxanes, leukotrienes) generated from arachidonic acid (AA) and eicosapentaenoic acid (EPA). The AA-derived mediators are generated from omega-6 fatty acid (FA) and have strong proinflammatory effects and the EPA-derived mediators generated from omega-3-fatty acid are less active or even exhibit anti-inflammatory effects. Basic parenteral nutrition delivers omega-6-FA and omega-3 FA at a ratio of approximately 7:1. **AIM:** To investigate whether altering the FA composition by fish oil supplementation (omega-3-FA) affects cytokine production and the parameters reflecting systemic disease severity in experimental AP. **METHODS:** Severe AP was induced in 30 rats by standardized intraductal infusion of bile salt and IV cerulein. Six hours after AP induction, rats were randomized to TPN using commercial solutions with identical amounts of glucose, amino acids, and fat but different FA compositions: group 1 received a soybean-based fat solution without additional fish oil and group 2 was supplemented with 0.2 g/kg per day fish oil. TPN was continued for two days. Serum concentrations of IL-6 and IL-10 were measured before and after AP induction and at 24 and 48 hours after starting TPN. Routine cardiorespiratory and renal parameters were monitored to assess the systemic response at the organ level. **RESULTS:** Animals treated with fish oil had significantly higher IL-10 values (at 24 hours, 63 +/- 7 versus 46 +/- 3 pg/mL), produced more urine (28 +/- 0.9 versus 21 +/- 1.6 mL), and had significantly fewer episodes of respiratory dysfunction (defined as a pO<sub>2</sub> < 80 mm Hg or pCO<sub>2</sub> > 50 mm Hg for >15 minutes; 29% versus 67%) during the observation period. **CONCLUSIONS:** Altering eicosanoid mediator precursor availability by infusion of (omega-3 fatty acid increases anti-inflammatory cytokines in this model of AP. This together with improved renal and respiratory function suggests that the systemic response to pancreatic injury is attenuated.

*JPEN J Parenter Enteral Nutr.* 2002 Nov-Dec;26(6):351-6

#### **Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women.**

The extent to which women of reproductive age are able to convert the n-3 fatty acid alpha-linolenic acid (ALNA) to eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) was investigated in vivo by measuring the concentrations of labeled fatty acids in plasma for 21 days following the ingestion of [U-<sup>13</sup>C]ALNA (700 mg). [<sup>13</sup>C] ALNA excursion was greatest in cholesteryl ester (CE) (224 (sem 70) micromol/l over 21 d) compared with triacylglycerol (9-fold), non-esterified fatty acids (37-fold) and phosphatidylcholine (PC, 7-fold). EPA excursion was similar in both PC (42 (sem 8) micromol/l) and CE (42 (sem 9) micromol/l) over 21 days. In contrast both [<sup>13</sup>C]DPA and [<sup>13</sup>C]DHA were detected predominately in PC (18 (sem 4) and 27 (sem 7) micromol/l over 21 days, respectively). Estimated net fractional ALNA inter-conversion was EPA 21%, DPA 6% and DHA 9%. Approximately 22% of administered [<sup>13</sup>C]ALNA was recovered as <sup>13</sup>CO<sub>2</sub> on breath over the first 24 hours of the study. These results suggest differential partitioning of ALNA, EPA and DHA between plasma lipid classes, which may facilitate targeting of individual n-3 fatty acids to specific tissues. Comparison with previous studies suggests that women may possess a greater capacity for ALNA conversion than men. Such metabolic capacity may be important for meeting the demands of the fetus and neonate for DHA during pregnancy and lactation. Differences in DHA status between women both in the non-pregnant state and in pregnancy may reflect variations in metabolic capacity for DHA synthesis.

*Br J Nutr.* 2002 Oct;88(4):411-20

#### **Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action.**

The role of marine fish oil (n-3) polyunsaturated fatty acids in the prevention of fatal ventricular arrhythmia has been established in experimental animals. Prevention of arrhythmias arising at the onset of ischemia and reperfusion is important because if untreated, they result in sudden cardiac death. Animals supplemented with fish oils in their diet developed little or no ventricular fibrillation after ischemia was induced. Similar effects have also been observed in cultured neonatal cardiomyocytes. Several mechanisms have been proposed and studied to explain the antiarrhythmic effects of fish oil polyunsaturated fatty acids, but to date, no definite mechanism has been validated. The sequence of action of these mechanisms and whether more than one mechanism is involved is also not clear. Some of the mechanisms suggested to explain the antiarrhythmic action of fish oils include the incorporation and modification of cell membrane structure by (n-3) polyunsaturated fatty acids, their direct effect on calcium channels and cardiomyocytes and their role in eicosanoid metabolism. Other mechanisms that are currently being investigated include the role of (n-3) polyunsaturated fatty acids in cell signalling mediated through phosphoinositides and their effect on various enzymes and receptors. This article reviews these mechanisms and the antiarrhythmic studies using (n-3) polyunsaturated fatty acids.

*J Nutr.* 1997 Mar;127(3):383-93

### **Supplementation with n-3 fatty acids in chronic inflammatory bowel disease—a randomized, placebo-controlled, double-blind cross-over trial.**

Thirty-nine patients with chronic inflammatory bowel disease were studied in a seven-month, double-blind, placebo controlled cross-over trial of dietary supplementation with fish oil, which provided about 3.2 g n-3 fatty acids per day. At control, biopsies from inflamed mucosa contained higher levels of arachidonic acid than uninvolved mucosa. Dietary n-3 fatty acids were well tolerated and incorporated into plasma and enteric mucosa phospholipids at the expense of n-6 fatty acids. The arachidonic acid-derived prostanoid generation was reduced by fish oil and the extension and severity of macroscopic bowel involvement was moderately improved. In patients with Crohn's disease, clinical activity was unchanged by fish-oil supplementation. In patients with ulcerative colitis, clinical disease activity fell during fish oil supplementation and thereafter; this was not significant however. Despite a moderate reduction in inflammatory lipid mediators by dietary n-3 fatty acids and limited morphological improvement in chronic inflammatory bowel disease, the clinical benefit seems to be confined to patients with ulcerative colitis.

*J Intern Med Suppl. 1989;225(731):225-32.*

### **Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group.**

**BACKGROUND:** Fatty acid research in schizophrenia has demonstrated an altered cell membrane phospholipid metabolism. Erythrocyte membrane phospholipid composition closely reflects that of neuronal membranes. **METHODS:** (Poly)(un)saturated fatty acid concentrations were measured in the erythrocyte membranes of 19, consecutively admitted, medicated young schizophrenic patients and then compared with matched control subjects. Psychiatric symptomatology was rated with the Positive and Negative Symptom Scale and Montgomery-Asberg Depression Rating Scale. Because diet, hormones, and cannabis influence fatty acid metabolism, we included these factors in our study. **RESULTS:** The most distinctive findings concerned the omega-3 series: C22:5 omega-3, C22:6 omega-3 (docosahexaenoic acid), and the sum of omega-3 fatty acids were significantly decreased. Interestingly, C20:4 omega-6 (arachidonic acid) was not lowered. In the omega-9 series, higher levels of C22:1 omega-9 and lower levels its elongation product, C24:1 omega-9 (nervonic acid), were found. Interestingly, the other arm of the desaturation-elongation sequence of C18:1 omega-9, C20:3 omega-9, was lower in patients. The total omega-9 fatty acid levels were also lower in patients. **CONCLUSIONS:** Significant differences in erythrocyte fatty acid composition were found. The differences were not due to diet or hormonal status and could not be explained by the medication or cannabis use. No consistent pattern emerged from the different fatty acid abnormalities and the clinical symptom scores.

*Biol Psychiatry. 2001 Mar 15;49(6):510-22*

### **Omega-3 but not omega-6 fatty acids inhibit AP-1 activity and cell transformation in JB6 cells.**

Epidemiological and animal-based investigations have indicated that the development of skin cancer is in part associated with poor dietary practices. Lipid content and subsequently the derived fatty acid composition of the diet are believed to play a major role in the development of tumorigenesis. Omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), can effectively reduce the risk of skin cancer whereas omega-6 (omega-6) fatty acids such as arachidonic acid (AA) reportedly promote risk. To investigate the effects of fatty acids on tumorigenesis, we performed experiments to examine the effects of the omega-3 fatty acids EPA and DHA and of the omega-6 fatty acid AA on phorbol 12-tetradecanoate 13-acetate (TPA)-induced or epidermal growth factor (EGF)-induced transcription activator protein 1 (AP-1) transactivation and on the subsequent cellular transformation in a mouse epidermal JB6 cell model. DHA treatment resulted in marked inhibition of TPA- and EGF-induced cell transformation by inhibiting AP-1 transactivation. EPA treatment also inhibited TPA-induced AP-1 transactivation and cell transformation but had no effect on EGF-induced transformation. AA treatment had no effect on either TPA- or EGF-induced AP-1 transactivation or transformation, but did abrogate the inhibitory effects of DHA on TPA- or EGF-induced AP-1 transactivation and cell transformation in a dose-dependent manner. The results of this study demonstrate that the inhibitory effects of omega-3 fatty acids on tumorigenesis are more significant for DHA than for EPA and are related to an inhibition of AP-1. Similarly, because AA abrogates the beneficial effects of DHA, the dietary ratio of omega-6 to omega-3 fatty acids may be a significant factor in mediating tumor development.

*Proc Natl Acad Sci U S A. 2001 Jun 19;98(13):7510-5*

### **Effect of an eight-month treatment with omega-3 fatty acids (eicosapentaenoic and docosahexaenoic) in patients with cystic fibrosis.**

**BACKGROUND:** Supplementation of the diet with eicosapentaenoic acid and docosahexaenoic acid, the main long-chain omega-3 fatty acids in cell membranes, may have beneficial effects in patients with cystic fibrosis. **METHODS:** A prospective study involving 30 patients and 20 control subjects was carried out; eicosapentaenoic plus docosahexaenoic acid was equal to 1.3% of caloric intake in the cystic fibrosis patients. Our present study included the evaluation of eicosapentaenoic and docosahexaenoic acid incorporation into erythrocyte membranes and biological and clinical effects in response to long-term (eight months) supplementation with fish oil as a source of eicosapentaenoic and docosahexaenoic acids in patients with cystic fibrosis. **RESULTS:** Baseline erythrocyte membrane fatty acids showed low levels of linoleic acid and eicosapentaenoic acid and mild elevation of 18:3n-6, but similar docosahexanoic acid and other fatty acids in cystic fibrosis patients compared with controls. Fish oil supplementation led to a 1.7-fold ( $p < .05$ ) and 1.3-fold (not significant) increase of eicosapentaenoic acid in erythrocyte membrane phospholipids after 4 and 8 months of supplementation, respectively, and to a 1.67-fold ( $p < .05$ ) and 1.38-fold ( $p$

< .05) increase of docosahexaenoic acid, respectively. Along with these changes, there was a progressive decrease of arachidonic acid (from 8.51 to 6.67 g/100 fatty acids at four months and 4.83 g/100 fatty acids at eight months;  $p < .05$ ) and an increase of linoleic acid ( $p < .05$ ) in membrane phospholipids. Analysis of inflammatory markers showed a significant decrease of serum immunoglobulin G (IgG) and of alpha-1 antitrypsin ( $p < .05$ ) concentrations. Pulmonary function testing showed mild but significant improvement of forced expiratory volume (FEV)-1 from 61% +/- 19% to 57% +/- 19% of predicted values ( $p < .05$ ). The number of days of antibiotic therapy during the study period was markedly lower compared with the preceding eight-month period (392 versus 721 days;  $p < .05$ ). **CONCLUSION:** Long-term eicosapentaenoic plus docosahexaenoic acid supplementation (eight months) has positive effects, such as decreasing inflammation, in cystic fibrosis.

*JPEN J Parenter Enteral Nutr.* 2003 Jan-Feb;27(1):52-7

## Homocysteine

### **Homocysteine as a risk factor for cognitive impairment in stroke patients.**

**BACKGROUND:** Elevated total homocysteine (tHcy) levels are associated with an increased risk of cerebrovascular disease. It is uncertain whether tHcy is also an independent risk factor for cognitive impairment. **METHODS:** We examined 95 stroke subjects three months after their strokes, and 55 healthy comparison subjects, with a detailed neuropsychological assessment, and MRI brain scans in a proportion ( $n = 97$ ). Baseline measurements of tHcy, serum folate and B(12), creatinine and plasma fibrinogen levels were obtained. **RESULTS:** tHcy levels were higher in the stroke subjects by a mean 34%. These levels were significantly correlated with the first factor of a principal component analysis of the neuropsychological data, after controlling for age, folate, B (12) and creatinine levels. The correlation of Hcy levels was particularly significant with frontal-executive functioning and attention. tHcy levels were significantly correlated with number of infarcts and total stroke volume in the stroke group, but not with T(2)-weighted deep white matter hyperintensity scores, after correction for age. In the control group, tHcy levels were significantly correlated with ventricle-to-brain ratios as measures of brain atrophy. **CONCLUSION:** This study provides evidence that high tHcy levels are associated with cognitive impairment, in particular that of frontal-executive function. The major component of this association is accounted for by small and large strokes, but non-vascular neurotoxic effects of tHcy also appear to play a role. tHcy must receive greater attention as a risk factor for cognitive impairment.

*Dement Geriatr Cogn Disord.* 2003;15(3):155-62

### **Plasma chain-breaking antioxidants in Alzheimer's disease, vascular dementia and Parkinson's disease.**

We studied the plasma chain-breaking antioxidants alpha carotene, beta carotene, lycopene, Vitamin A, Vitamin C, Vitamin E and a measure of total antioxidant capacity, TAC, in 79 patients with Alzheimer's disease (AD), 37 patients with vascular dementia (VaD), 18 patients with Parkinson's disease and dementia (PDem), and 58 matching controls, together with 41 patients with Parkinson's disease (PD) and 41 matching controls. Significant reductions in individual antioxidants were observed in all dementia groups. When compared to controls, the following were reduced: Vitamin A in AD ( $p < 0.01$ ) and VaD ( $p < 0.001$ ); Vitamin C in AD ( $p < 0.001$ ), VaD ( $p < 0.001$ ) and PDem ( $p < 0.01$ ); Vitamin E in AD ( $p < 0.01$ ) and VaD ( $p < 0.001$ ); beta carotene in VaD ( $p = 0.01$ ); lycopene in PDem ( $p < 0.001$ ). Lycopene was also reduced in PDem compared to AD ( $p < 0.001$ ) and VaD ( $p < 0.001$ ). Antioxidant levels in PD were not depleted. No significant change in TAC was seen in any group. The reduction in plasma chain-breaking antioxidants in patients with dementia may reflect an increased free-radical activity, and a common role in cognitive impairment in these conditions. Increased free-radical activity in VaD and PDem could be associated with concomitant AD pathology. Individual antioxidant changes are not reflected in TAC.

*QJM.* 1999 Jan;92(1):39-45

### **Alzheimer's disease: protective factors.**

Approximately 6-8% of all persons aged >65 years have Alzheimer's disease and the prevalence of the disease is increasing. Any intervention strategy aimed at decreasing risks or delaying the onset of the disease will therefore have a substantial effect on health care costs. Nutrition seems to be one of the factors that may play a protective role in Alzheimer's disease. Many studies suggest that oxidative stress and the accumulation of free radicals are involved in the pathophysiology of the disease. Several studies have shown the existence of a correlation between cognitive skills and the serum concentrations of folate, vitamin B-12, vitamin B-6, and, more recently, homocysteine. However, nutritional factors have to be studied not alone but with the other factors related to Alzheimer's disease: genetics, estrogen, antiinflammatory drug use, and socioeconomic variables. The objective of this article was to review recent studies in this field.

*Am J Clin Nutr.* 2000 Feb;71(2):643S-649S

### **Homocysteine and Alzheimer's disease.**

**BACKGROUND:** A high circulating concentration of the amino acid homocysteine is an independent risk factor for stroke. Alzheimer's disease (AD) commonly co-occurs with stroke. Epidemiological studies found associations between hyperhomocysteinaemia and both histologically confirmed AD and disease progression and revealed that dementia in AD was associated with evidence of brain infarcts on autopsy. Thus, hyperhomocysteinaemia and AD could be linked by stroke or

microvascular disease. However, given known relations between B-group-vitamin deficiency and both hyperhomocysteinaemia and neurological dysfunction, direct causal mechanisms are also plausible. RECENT DEVELOPMENTS: A recent prospective study (S. Seshadri and colleagues *N Engl J Med*; 2002 346: 476-83) showed hyperhomocysteinaemia to be a strong, independent risk factor for dementia and AD. The researchers found a graded increase in risk of both outcomes with rising plasma concentration of homocysteine after multivariate control for putative risk factors for AD. In conjunction with demonstration of a fall in homocysteine concentrations in response to increasing B-group-vitamin status, these findings give hope that mental decline, or AD itself, could be prevented by dietary modification or food fortification. WHERE NEXT? 25% of dementia cases are attributed to stroke. The possibility that some of the other 75% might be prevented by the lowering of homocysteine concentrations greatly increases the hope of maintaining self-sufficiency into old age. If homocysteine lowering can reduce the incidence of dementia or AD, decreased incidence of these disorders may be seen in Canada and the USA, where government-mandated folate-fortification programmes are in effect. Future research should focus on early detection of AD and on the possibility that the disease itself, or its primary symptom, could be prevented by folate supplementation.

*Lancet Neurol.* 2003 Jul;2(7):425-8

### **Plasma total homocysteine in a representative sample of 972 British men and women aged 65 and over.**

**OBJECTIVES:** To provide a reference range for plasma total homocysteine (tHcy), an independent risk factor for vascular disease, and to explore relationships with nutritional indices for people aged 65 years and over, in the UK National Diet and Nutrition Survey (NDNS). **DESIGN:** The survey procedures described in the National Diet and Nutrition Survey Report (1997) included a health-and-lifestyle interview, a four-day weighed diet record, anthropometric and blood pressure measurements and a fasting blood sample for biochemical indices, including tHcy. **SETTING:** Eighty randomly selected postcode sectors from mainland Britain during 1995-1996. **SUBJECTS:** Of 2,060 people interviewed, 1,527 were visited by the nurse, 1,276 gave a blood sample and 972 had tHcy measured. About 80% were in their own homes and the remainder were in nursing homes or similar institutions. **RESULTS:** Significant cross-sectional relationships, both univariate and multivariate were found between tHcy and index concentrations of folate and vitamin B12 ( $P < 0.0001$ ), and between tHcy and plasma creatinine, urea, calcium, zinc, alpha 1-antichymotrypsin, lutein and cysteine ( $P = 0.013$  to  $< 0.0001$ ). Dietary nutrient analyses showed an association with folate intake. tHcy was also correlated with age and with domicile (free-living or institution), with history of vascular disease and with use of four classes of drugs, two of which are prescribed for vascular diseases. There was a north-south gradient in tHcy ( $P = 0.005$ ), and also in food choices, blood micronutrient indices and vascular disease prevalence. **CONCLUSIONS:** The concentrations of tHcy found in this study provide a reference range for people aged 65 years and over, in mainland Britain. tHcy is a valuable functional index of micronutrient status and intakes for British people aged 65 years and over, which can assist the development of health-promotion strategies.

*Eur J Clin Nutr.* 1997 Oct;51(10):691-7

### **Homocysteine: a marker for cognitive performance? A longitudinal follow-up study.**

The present prospective study investigated whether elevated total serum homocysteine concentration is a risk factor for cognitive decline. The outcomes were compared to the possible relation between cognition and vitamin B12 or folic acid. Cognitive performance of 144 normal aging individuals (aged 30-80 years) was tested at baseline and after six years of follow-up. Domains of cognitive function addressed were cognitive speed (Letter-Digit Coding test), attention and information processing (Stroop test) and verbal learning and memory (Word Learning Test Total; Delayed Recall). Serum concentrations of homocysteine, folic acid and vitamin B12 were determined. Serum concentrations of homocysteine correlated negatively with cognitive performance on the Word Learning tests at baseline, independent of age, sex, education level or folic acid concentration. Homocysteine concentration at baseline correlated negatively with cognitive performance on the Stroop and Word Learning tests during the whole six-year follow-up period. The folic acid concentration correlated to the Delayed Recall test at baseline only and no correlations were observed for vitamin B12. Thus, while a relation between vitamin B12 or folic acid and cognition was almost absent, elevated homocysteine concentrations were associated with prolonged lower cognitive performance in this normal aging population.

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