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Homocysteine: update on a new risk factor.

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Cleve Clin J Med (United States) Nov-Dec 1997, 64 (10) p543-9

A high fasting plasma homocysteine level is an independent risk factor for atherosclerosis and venous thrombosis . Vitamin therapy can lower homocysteine levels, but no benefit has yet been demonstrated; studies using clinical outcomes as endpoints are now in progress. (34 Refs.)

Total plasma antioxidant capacity predicts thrombosis-prone status in NIDDM patients.

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Diabetes Care (United States) Oct 1997, 20 (10) p1589-93

OBJECTIVE: To explore the hypothesis that a relationship exists between free radical activity and abnormalities in hemostasis in NIDDM.

RESEARCH DESIGN AND METHODS: The use of the total radical-trapping antioxidant parameter (TRAP) has very recently been proposed to explore the antioxidant property of a plasma and their mutual cooperation. In the present study, TRAP, vitamin E, vitamin C, vitamin A, uric acid, protein-bound SH (thiol) groups, fibrinogen, prothrombin fragments F1 + 2, and D-dimer have been evaluated in 46 NIDDM patients and 47 healthy matched control subjects.

RESULTS: In NIDDM patients, TRAP, vitamin A, SH groups, and uric acid were significantly reduced, whereas the level of vitamin E was significantly increased. Vitamin C was similar in the two groups. Fibrinogen, prothrombin fragment 1 + 2, and D-dimer were increased in diabetic patients. TRAP, but no single other antioxidant, had a strong inverse association with fibrinogen, prothrombin fragment 1 + 2, and D-dimer.

CONCLUSIONS: These findings are consistent with the hypothesis that oxidative stress may condition coagulation activation in diabetics. However, the data suggest that it is the total antioxidant capacity rather than any single plasma antioxidant that is the most relevant parameter.

Effects of dietary fat quality and quantity on postprandial activation of blood coagulation factor VII.

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Arterioscler Thromb Vasc Biol (United States) Nov 1997, 17 (11) p2904-9

Acute elevation of the coagulant activity of blood coagulation factor VII (FVIIc) is observed after consumption of high-fat meals. This elevation is caused by an increase in the concentration of activated FVII (FVIIa). In a randomized crossover study, we investigated whether saturated, monounsaturated, or polyunsaturated fats differed regarding postprandial activation of FVII. Eighteen healthy young men participated in the study. On 6 separate days each participant consumed two meals (times, 0 and 1 3/4 hours) enriched with 70 g (15 and 55 g) of either rapeseed oil, olive oil, sunflower oil, palm oil, or butter (42% of energy from fat) or isoenergetic low-fat meals (6% of energy from fat). Fasting and series of nonfasting blood samples (the last at time 8 1/2 hours)

were collected. Plasma triglycerides, FVIIc, FVIIa, and free fatty acids were analyzed. There were marked effects of the fat quantity on postprandial responses of plasma triglycerides, FVII, and free fatty acids. The high-fat meals caused, in contrast to the low-fat meals, considerable increases in plasma triglycerides. Plasma levels of FVIIc and FVIIa peaks were 7% and 60% higher after consumption of high-fat meals than after consumption of low-fat meals. The five different fat qualities caused similar postprandial increases in plasma triglycerides, FVIIc, and FVIIa. These findings indicate that high-fat meals may be prothrombotic, irrespective of their fatty acid composition. The postprandial FVII activation was not associated with the plasma triglyceride or free fatty acid responses.

Hyperhomocysteinaemia in black patients with cerebral thrombosis.

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QJM (England) Oct 1997, 90 (10) p635-9

Hyperhomocysteinemia is regarded as a risk factor for stroke but its pathogenetic role has not yet been established in Black patients. We studied 24 Black patients admitted with cerebral thrombosis, and compared them with age- and sex-matched apparently healthy controls from the same community. Total homocysteine (tHcy) (free homocysteine, protein-bound homocysteine, the disulfide homocystine and the mixed disulfide homocysteine-cysteine) concentration was 10.91 (4.95-23.05) mumol/l in the stroke patients and 8.73 (3.95-15.10) mumol/l in controls (p = 0.031). This difference could not be explained by differences in vitamin B12, vitamin B6 or folate status. A subgroup of nine stroke patients with hypercreatininaemia (> 90 mumol/l, 75% of control concentrations) had significantly higher plasma tHcy concentrations [median (range) 9.10 (5.40-15.10) mumol/l] compared with controls [8.65 (3.96-13.89) mumol/l] (p = 0.002). Plasma tHcy concentrations of stroke patients with normal serum creatinine concentrations were not significantly different to those of controls. Hyperhomocysteinemia in Black patients with stroke may be partially caused by renal insufficiency. Therefore, while hyperhomocysteinemia may increase the risk of stroke, it is unlikely to be a primary initiating factor.

High antibody levels to prothrombin imply a risk of deep venous thrombosis and pulmonary embolism in middle-aged men--a nested case-control study.

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Thromb Haemost (Germany) Oct 1997, 78 (4) p1178-82

Antibodies against phospholipid-binding plasma proteins, such as beta2-glycoprotein I (beta2-GPI) and prothrombin, are associated with thromboembolic events in patients with systemic lupus erythematosus and also in subjects with no evident underlying diseases. We wanted to examine whether increased levels of antibodies to negatively-charged phospholipids (cardiolipin), to phospholipid-binding plasma proteins beta2-GPI and prothrombin and to oxidised low-density lipoprotein (LDL) were associated with risk of deep venous thrombosis or pulmonary embolism in subjects with no previous thrombosis . The antibodies were measured in stored serum samples from 265 cases of deep venous thrombosis of the lower extremity or pulmonary embolism occurring during a median follow-up of about 7 years and from 265 individually matched controls. The study subjects were middle-aged men participating in a cancer prevention trial of alpha-tocopherol and beta-carotene and the cases of thromboembolic events were identified from nationwide Hospital Discharge Register. The risk for thrombotic events was significantly increased only in relation to antiprothrombin antibodies. As adjusted for body mass index, number of daily cigarettes and history of chronic bronchitis, myocardial infarction and heart failure at baseline, the odds ratio per one unit of antibody was 6.56 (95% confidence interval 1.73-25.0). The seven highest individual optical density-unit values of antiprothrombin antibodies were all confined to subjects with thromboembolic episodes. In conclusion, the present nested case-control study showed that high autoantibody levels against prothrombin implied a risk of deep venous thrombosis and pulmonary embolism and could be involved in the development of the thrombotic processes.

Plasminogen activator inhibitor-1, the acute phase response and vitamin C.

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Atherosclerosis (Ireland) Aug 1997, 133 (1) p71-6

Epidemiologial studies suggest that elevated plasma plasminogen activator inhibitor-1 (PAI-1) activity is associated with ischaemic heart disease. Based on our earlier work suggesting a link between plasma fibrinogen, infection and low vitamin C status, we sought to determine whether similar relationships existed for PAI-1 activity. We performed a longitudinal study of cardiovascular disease risk factors in 96 volunteers aged 65-74 years, living in the community in Cambridge. Each subject was visited at home 7 times over a 14 month period. Plasma PAI-1 activity, serum ascorbate, markers of the acute phase response, serum lipids and other cardiovascular disease risk factors were measured on each occasion. In a multiple regression analysis, the three significant predictors of PAI-1 activity were body mass index (P = 0.0001), blood neutrophil count (P = 0.03) and, inversely, serum ascorbate (P = 0.003). The inverse relationship between PAI-1 activity and serum ascorbate persisted even when vitamin C supplement takers or smokers were excluded from the analysis. Serum ascorbate was strongly related to estimated dietary intake of vitamin C (P <001). Low serum ascorbate is associated with high PAI-1 activity which is, in turn, associated with increased ischaemic heart disease risk. We hypothesise that activation of the acute phase response by infection could increase PAI-1 activity and, consequently, also increase the risk of coronary artery thrombosis . Furthermore, we suggest that vitamin C could attenuate this response.

Hyperhomocysteinemia and thrombosis: acquired conditions.

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Thromb Haemost (Germany) Jul 1997, 78 (1) p527-31

Hyperhomocysteinemia is a condition which, in the absence of kidney disease, indicates a disrupted sulfur amino acid metabolism, either because of vitamin (folate, B12 and B6) deficiency or a genetic defect. Epidemiological evidence suggests that mild hyperhomocysteinemia is associated with increased risk of arteriosclerotic disease and stroke. The relationship between hyperhomocysteinemia and thrombosis has been investigated in 10 studies involving a total of 1200 patients and 1200 controls. Eight of these studies demonstrated positive association with odds ratios that ranged from 2 to 13. This association was enhanced by including a methionine loading test. There is some evidence which suggests that hyperhomocysteinemia and APC resistance have a synergistic effect on the onset of thrombotic disease. Studies on the mechanism that underlies the relationship between thrombosis and hyperhomocysteinemia used non-physiologically high levels of homocysteine, rendering the data doubtful as to their patho-physiological relevance. (24 Refs.)

Hyperhomocysteinemia as a risk factor for arterial and venous disease. A review of evidence and relevance.

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Thromb Haemost (Germany) Jul 1997, 78 (1) p520-2

In homozygous homocystinuria due to cystathionine synthase deficiency, characterized by severe hyperhomocysteinemia, there is a high incidence of vascular complications. These observations focus on homocysteine as an atherogenic and thrombophilic agent. At the present time, there is also convincing evidence that even mild hyperhomocysteinemia is a risk factor for cardiovascular disease due to occlusive arterial complications. Furthermore, a positive association between mild hyperhomocysteinemia and the occurrence of venous thrombosis has been shown but needs further study. Mildly elevated homocysteine levels affect the arterial system independently from conventional risk factors. This newly- recognized factor seems equally strong in risk to hypercholesterolemia and smoking, while hypertension leads to a larger excess risk. It interacts synergistically with hypertension and smoking in a joint arteriosclerotic effect in patients with the concomitant presence of these risk factors. The homocysteine-lowering efficacy of a simple and safe vitamin regimen has been proven but data on the clinical outcome of such intervention are lacking thus far. (25 Refs.)

Homocysteine in Greenland Inuits.

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Thromb Res (United States) May 15 1997, 86 (4) p333-5

Patients with homozygous homocystinuria are at greatly increased risk for development of atherosclerosis and thrombosis (1).

Elevated plasma levels of homocysteine (HCY) are caused by reduced enzymatic catabolism or reduced enzymatic remethylation of HCY, due to either hereditary enzyme defects or to nutritional deficiencies of vitamins functioning as cofactors. However, several recent studies have suggested that persons with mildly elevated plasma levels of HCY also are at increased risk for coronary heart disease. (2-4). There are some indications that dietary n-3 polyunsaturated fatty acids (PUFAs) may offer protection against coronary heart disease (5-6). Several mechanisms may be involved, including beneficial effects of n-3 PUFAs on plasma lipids, platelet and leukocyte reactivity, blood pressure and vasoreactivity (7). Interestingly, Olszewski el al. recently found HCY-levels to be lowered 36% in 15 type IIa or IIb hyperlipemic men by n-3 PUFA supplementation. A possible beneficial effect of n-3 PUFA on the incidence of coronary heart disease was initially suggested from studies in Greenland Inuits by our group (8). We therefore investigated plasma levels of homocysteine in a group of traditionally living Greenland Inuits with a diet consisting mainly of marine food and with a very high content of n-3 PUFAs.

Homocysteine, oxidative stress, and vascular disease

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Hosp Pract (Off Ed) (United States) Jun 15 1997, 32 (6) p81-2, 85

First recognized in patients with rare inborn errors of metabolism, the association of elevated plasma homocysteine concentrations with atherosclerosis and thrombosis now seems relevant to the general population as well. The mechanism of injury appears to involve oxidative damage to endothelial cells. Vitamin supplementation can normalize homocysteine levels and may lower the incidence of atherothrombotic vascular disease. (13 Refs.)

Hyperhomocysteinemia and venous thromboembolic disease.

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Haematologica (Italy) Mar-Apr 1997, 82 (2) p211-9

BACKGROUND AND OBJECTIVE: In spite of the large number of reports showing that hyperhomocysteinemia (HHcy) is an independent risk factor for atherosclerosis and arterial occlusive disease, this metabolite of the methionine pathway is measured in relatively few laboratories and its importance is not fully appreciated. Recent data strongly suggest that mild HHcy is also involved in the pathogenesis of venous thromboembolic disease. The aim of this paper is to analyze the most recent advances in this field.

EVIDENCE AND INFORMATION SOURCES: The material examined in the present review includes articles and abstracts published in journals covered by the Science Citation Index and Medline. In addition the authors of the present article have been working in the field of mild HHcy as cause of venous thromboembolic disease.

STATE OF ART AND PERSPECTIVES: The studies examined provide very strong evidence supporting the role of moderate HHcy in the development of premature and/or recurrent venous thromboembolic disease. High plasma homocysteine levels are also a risk factor for deep vein thrombosis in the general population. Folic acid fortification of food has been proposed as a major tool for reducing coronary artery disease mortality in the United States. Vitamin supplementation may also reduce recurrence of venous thromboembolic disease in patients with HHcy. At the present time, however, the clinical efficacy of this approach has not been tested. In addition, the bulk of evidence indicates that fasting total homocysteine determinations can identify up to 50% of the total population of hyperhomocysteinemic subjects. Patients with isolated methionine intolerance may benefit from vitamin B6 supplementation. Homocysteine-lowering vascular disease prevention trials are urgently needed. Such controlled studies, however, should not focus exclusively on fasting homocysteine determinations and folic acid monotherapy. (127 Refs.)

Diet and haemostasis: time for nutrition science to get more involved.

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Br J Nutr (England) May 1997, 77 (5) p671-84

Abnormal haemostasis, and specifically a pre-thrombotic state characterized by hypercoagulability, increased platelet aggregation and impaired fibrinolysis, is associated with increased atheroma and thrombosis . The recent literature clearly indicates that diet

may prevent or be used to treat some abnormal haemostatic states. There are reports on effects of energy intake and expenditure, alcohol consumption, intakes of total fat, different fatty acids, fish oil, NSP and vitamins on markers of coagulation, platelet function and fibrinolysis. Some of the confusion and controversy in this field has arisen because the wrong markers of haemostasis have been measured in dietary trials. Moreover, many of the studies have lacked good dietary control. It is suggested that more sensitive, functional markers of the balance between the different facets of the haemostatic system should be measured. It is also important to test hypotheses developed from known observations and to propose mechanisms of action of the various dietary factors, based on our improved understanding of the haemostatic system. (103 Refs.)

Homocyst(e)ine: an important risk factor for atherosclerotic vascular disease.

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Curr Opin Lipidol (United States) Feb 1997, 8 (1) p28-34

Homocysteine is an intermediate compound formed during metabolism of methionine. The results of many recent studies have indicated that elevated plasma levels of homocyst(e)ine are associated with increased risk of coronary atherosclerosis, cerebrovascular disease, peripheral vascular disease, and thrombosis . The plasma level of homocyst(e)ine is dependent on genetically regulated levels of essential enzymes and the intake of folic acid, vitamin B6 (pyridoxine), and vitamin B12 (cobalamin). Impaired renal function, increased age, and pharmacologic agents (e.g. nitrous oxide, methotrexate) can contribute to increased levels of homocyst(e)ine. Plausible mechanisms by which homocyst(e)ine might contribute to atherogenesis include promotion of platelet activation and enhanced coagulability, increased smooth muscle cell proliferation, cytotoxicity, induction of endothelial dysfunction, and stimulation of LDL oxidation. Levels of homocysteine can be reduced with pharmacologic doses of folic acid, pyridoxine, vitamin B12, or betaine, but further research is required to determine the efficacy of this intervention in reducing morbidity and mortality associated with atherosclerotic vascular disease. (86 Refs.)

High plasma homocysteine: A risk factor for arterial and venous thrombosis in patients with normal coagulation profiles

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Clinical and Applied Thrombosis/Hemostasis (United States), 1997, 3/4 (239-244)

A high plasma homocysteine concentration is associated with premature vascular disease and thrombosis . The association between high homocysteine concentrations and thrombosis in patients with a normal coagulation profile is unknown. Sixty adults (37 men and 23 women, mean age 46 years) with documented thrombosis were compared with age- and sex-matched controls. Those with risk factors for thrombosis or abnormal coagulation profiles were excluded. Homocysteine concentrations were higher in cases than controls (21.8 plus or minus 13.8 vs 11.0 plus or minus 4.7 micromol/L, $p < 0.001$). A cut point for defining high homocysteine concentrations was determined at 13 micromol/L and conferred an increased odds ratio for thrombosis overall (7.8, 95% CI 3.0-20.2, $p < 0.001$) as well as in men (8.9, 95% CI 3.026.1; $p < 0.001$) and women (37.8, 95% CI 6.5-213.9; $p < 0.01$). A high plasma homocysteine is a risk factor for thrombosis in patients with a normal coagulation profile. This common abnormality should be sought in patients with otherwise unexplained thrombotic episodes.

Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors

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Arteriosclerosis, Thrombosis, and Vascular Biology (United States), 1997, 17/12 (3449-3460)

Modification of dietary fat composition may influence hemostatic variables, which are associated with increased risk of coronary heart disease (CHD). To address this question, we performed a controlled feeding study on 26 healthy male nonsmoking subjects with diets of differing fat composition. For the first 3 weeks, the subjects were given a diet calculated to supply 30% energy as total

fat: 8% as monounsaturated, 4% as polyunsaturated, and 16% energy as saturated fatty acids, respectively (saturated diet). This was followed immediately by two diets taken in random order, each of 3-week duration and separated by an 8-week washout period on the subject's usual diet. Both diets were calculated to supply 30% of energy as fat: 14% monounsaturated, 6% as polyunsaturated, and 8% energy as saturated fatty acids. They both provided 5 g (approximately 1.7% energy) more of polyunsaturated fatty acids than the saturated fat diet; in one diet as long- chain n-3 fatty acids (n-3 diet) and in the other as linoleic acid (n-6 diet). Fasting plasma lipids, lipoproteins, and hemostatic factors were measured on the final 3 days of each dietary period. In a subset of 9 subjects the postprandial responses to a test meal were studied on the penultimate day of each period, each meal having the fat composition of its parent diet. On the n-3 diet compared with the n-6 diet, plasma triglyceride, HDL3 cholesterol, apoprotein AII, and fibrinogen concentrations were lower and HDL2 cholesterol concentration was higher (P=.0001, P=.003. P=.0001, P=.004 and P = .001, respectively). On both the n-3 and n-6 diets compared with the saturated diet, fasting plasma total and LDL cholesterol, apoprotein B, beta-thromboglobulin concentrations, and platelet counts were lower (P<.0001, P<.0001, P<.001, P<.01, and P<.05 respectively) and plasma Lp(a) and von Willebrand factor concentrations were higher (P=.02 and P<.01, respectively). Fasting factor VII coagulant activity (VIIc) was increased and apoprotein AI concentration reduced following the n-3 diet (P=.004 and P=.01, respectively) compared with the saturated diet. Plasma fibrinogen concentration was significantly greater following the n-6 diet than on the saturated diet (P=.02). Postprandially, plasma triglyceridemia was greater on the n-6 diet and lowest on the n-3 diet (P<.001) with the saturated diet being intermediate. Plasma VIIc was increased at 4 hours following the standardized test meals on the n-3 and n-6 diets (both P<.05) but not on the saturated diet. An increased intake of long chain n-3 fatty acids decreases fasting plasma triglyceride and apoprotein AII concentrations and increases HDL2 cholesterol concentrations and results in less postprandial lipemia but leads to an increase in VIIc. An increased intake of linoleic acid may raise plasma fibrinogen concentration. Decreasing the intake of saturated fatty acids reduces plasma LDL cholesterol and apoprotein B without affecting HDL cholesterol concentration independent of the type of polyunsaturated fatty acids in the diet. When advice is given to reduce saturated fat intake, it is important to ensure an appropriate ratio of n-3/n-6 fatty acids in the diet.

Fatty acids, triglycerides and syndromes of insulin resistance

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Prostaglandins Leukotrienes and Essential Fatty Acids (United Kingdom), 1997, 57/4-5 (379-385)

Muscle plays a major role in insulin-stimulated glucose disposal. There is now a range of evidence in humans and experimental animals demonstrating strong relationships between the fatty acid composition of structural membrane lipids and insulin action. The in vivo work is correlative but the in vitro studies suggest a causal relationship exists. Good insulin action is associated with an increased proportion of n-3 fatty acids, low saturates, a low n-6/n-3 ratio and possibly increased monounsaturates. What is reassuring is that there is a pleasing symmetry with the fatty acid pattern that might lead to decreased thrombosis . There is little argument about saturated fats with a reduction having a range of beneficial effects. However, the n-3 fatty acids might also be a key to amelioration of both insulin resistance and thrombosis . The sites of action of n-3s are multiple: decreased triglyceride and VLDL production; inhibition of thromboxane A2 production, increased thromboxane A3 and decreased platelet aggregation; reduction of triglyceride and VLDL concentration; improved blood theology and membrane transport; action on the endothelium and proliferation of the intimal cells, and improvement of vascular tone. The data here are now strong and reasonably consistent. Similarly, after initial controversy, the evidence for n-3s playing a beneficial role in insulin action is now accumulating. The n-6 PUFAs are a bit of a worry: while arachidonic acid levels in muscle phospholipid has linked positively to insulin action in our studies, linoleic is negative. Linoleic acid, in high amounts, is known to inhibit the Delta6 fatty acid desaturase enzyme and with the competition between n-6 and n-3 fatty acids for the enzymes of desaturation and elongation it does focus on a high n-6/n-3 ratio as a critical factor in both insulin resistance and atherosclerosis.

Hyperhomocysteinemia: A risk factor for arterial and venous thrombosis

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Annali Italiani di Medicina Interna (Italy), 1997, 12/3 (160-165)

In the lost two decades, retrospective case-control studies and prospective cohort studies have demonstrated that moderate hyperhomocysteinemia is a frequent and independent risk factor for premature vascular disease in the coronary, cerebral and peripheral arteries. More recently, the association of moderate hyperhomocysteinemia with venous thrombosis has been shown. Genetic and environmental factors act in concert to cause moderate hyperhomocysteinemia. Since inadequate intake of folic acid, vitamin B12 or vitamin B6 are most frequently associated with hyperhomocysteinemia, particularly in the elderly, it is likely that dietary supplementation of these vitamins could have a tremendous impact on the epidemiology and natural history of thrombotic

diseases.

Dietary fatty acids and arteriosclerosis

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Biomedicine and Pharmacotherapy (France), 1997, 51/8 (333-336)

Dietary fatty acids show different molecular structures and thus physicochemical properties of importance regarding lipid metabolism and atherogenesis. Intake of dietary fatty acids is associated with several risk factors for arteriosclerosis including fasting and postprandial plasma lipids and lipoproteins, obesity and thrombosis . Consumption of saturated fatty acids is detrimental while that of monounsaturated and polyunsaturated fatty acids lowers the incidence of coronary heart disease, but the respective influence of the various unsaturated fatty acids ingested is still discussed. The importance of the interaction between the human gene pool and dietary fatty acids is emerging.

Relation of plaque lipid composition and morphology to the stability of human aortic plaques

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Arteriosclerosis, Thrombosis, and Vascular Biology (USA), 1997, 17/7 (1337-1345)

The propensity of atherosclerotic plaques to disrupt may be influenced by their lipid content and the distribution of these lipids within the plaque. To investigate this, we analyzed the morphological and lipid profiles of 668 human aortic plaques from 30 males who had died of ischemic heart disease. Plaques were classified as disrupted or as intact types A or B, the latter distinction being based on the absence or presence, respectively, of disrupted plaques within the same aorta. Disrupted plaques have a greater content of lipid ($P<.001$) and macrophages ($P<.001$) as well as a thinner cap ($P<.001$) than intact plaques. Lipid concentrations are positively associated with macrophage accumulation in all plaque types and are negatively associated with minimum cap thickness at the edge of disrupted plaques ($P<.05$). Free cholesterol concentration is inversely associated with minimum cap thickness at the center of type B plaques only ($P<.05$). At the center of intact type A and B and disrupted plaques, the free-to-esterified cholesterol ratios were 0.9 (range, 0.0 to 2.7), 0.8 (0.0 to 3.9), and 1.6 (0.2 to 4.0), respectively. Esterified cholesterol concentrations were higher at the center of type B plaques, and those of free cholesterol were higher at the center of disrupted plaques. At the edge of disrupted plaques, the free-to-esterified cholesterol ratio was 0.5 (0.0 to 2.7) because of the accumulation of esterified cholesterol. Concentrations of all fatty acids were increased at the edge of disrupted plaques compared with the center, but as a proportion of total fatty acids, omega6-polyunsaturated fatty acids (PUFAs) were lower (44% versus 46%, $P<.01$), possibly reflecting oxidation of PUFAs. These data demonstrate differences in lipid composition and intraplaque lipid distribution between intact and disrupted plaques. At the edge of advanced plaques, increased esterified lipid concentrations, inversely associated with cap thickness, may reflect macrophage activity and predisposition to rupture.

Antioxidants and atherosclerotic heart disease

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New England Journal of Medicine (USA), 1997, 337/6 (408-416)

Epidemiologic studies have provided evidence of an inverse relation between coronary artery disease and antioxidant intake, and vitamin E supplementation in particular. The oxidative-modification hypothesis implies that reduced atherosclerosis is a result of the production of LDL that is resistant to oxidation, but linking the reduced oxidation of LDL to a reduction in atherosclerosis has been problematic. Several important additional mechanisms may underlie the role of antioxidants in preventing the clinical manifestations of coronary artery disease (Fig. 2). Specifically, there is evidence that plaque stability, vasomotor function, and the tendency to thrombosis are subject to modification by specific antioxidants. For example, cellular antioxidants inhibit monocyte adhesion, protect against the cytotoxic effects of oxidized LDL, and inhibit platelet activation. Furthermore, cellular antioxidants protect against the endothelial dysfunction associated with atherosclerosis by preserving endothelium- derived nitric oxide activity. We speculate that these mechanisms have an important role in the benefits of antioxidants.

The effect of short-term diets rich in fish, red meat, or white meat on thromboxane and prostacyclin synthesis in humans

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Lipids (USA), 1997, 32/6 (635-644)

Foods which increase tissue arachidonic acid levels have been proposed to increase thrombosis tendency, presumably through increased platelet aggregation. This study examined the effect of doubling the dietary arachidonic acid (20:4n-6) using meat- or fish based diets on the systemic production of prostacyclin (PGI2) and thromboxane (TXA2) in 29 healthy, nonsmoking adults. There were three, 3-wk low-fat dietary periods (<15% energy as fat) in which subjects consumed a vegetarian diet for 1 wk followed by 2 wk on diets containing meat or fish as sources of 20:4n-6. Between each diet period, there was a 3-wk washout period, during which subjects returned to their normal diets. The level of 20:4n-6 consumed during the last 2 wk of each study was approximately double the usual intake (mean 140 mg/d), while the mean eicosapentaenoic acid (20:5n-3) content of the diets varied from 1 mg/d on the white meat diet to 70 mg/d on the red meat diet and to 847 mg/d on the fish diet. The serum phospholipid (PL) 20:4n6/20:5n-3 ratios were 11:1 on the vegetarian diet, 15:1 on the white meat diet, 8:1 on the red meat diet, and 2:1 on the fish diet ($P < 0.001$). Neither white nor red meat diets affected platelet 20:4n-6 levels, platelet aggregation, ex vivo) platelet TXB2 production, or the systemic PGI2 or TXA2 production as measured by gas chromatography mass spectrometry analysis of the excretion levels of the principal urinary metabolites 2,3-dinor-6-keto-PGF(1alpha) (PGI2-M) and 11 dehydro-TXB2 (TXA2-M), respectively. The fish diet decreased the 20:4n- 6/20:5n-3 ratio in platelet PL from the baseline level of 45:1 to 13:1 ($P < 0.001$), had no effects on platelet aggregation, but significantly de creased platelet TXB2 production (collagen stimulated) and TXA2-M production, while PGI2-M levels were unaltered. These results indicate that short-term diets which double the usual 20:4n-6 intake using white meat (175-330 g/d) or red meat (275-530 g/d) are not associated with an increased TXA2 production, but this does not rule out the adverse effects of 20:4n6 at higher levels in the diet, or for more prolonged periods. Short-term diets containing fish (100- 200 g/d with 90-210 mg/d 20:4n-6 and approximately 650-1000 mg/d 20:5n-3) led to significant increases in platelet 20:5n-3 levels and a decrease in the ex vivo and systemic TXA2 production.

Purple grape juice has a significant platelet inhibitory effect

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American Family Physician (USA), 1997, 55/7 (2507-2508)

No abstract.

Dietary fatty acids in human thrombosis and hemostasis

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American Journal of Clinical Nutrition (USA), 1997, 65/5 Suppl. (1687S-1698S)

The effects of fatty acids on hemostasis are controversial. It has been difficult to show convincing effects of saturated or monounsaturated fatty acids that are clearly related to hemostatic variables in humans. Unsaturated fatty acids alter platelet aggregation and processes related to coagulation and fibrinolysis. Indirect evidence exists that n-6 polyunsaturated fatty acids may exert favorable effects on thrombotic processes in vivo, but large clinical trials have failed to show benefits of 5-6 g linoleic acid (18:2n-6) or linolenic acid (18:3n-3)/d. Only long- chain n-3 fatty acids prolong the template bleeding time, and they may exert some beneficial effect on erythrocyte flexibility. It appears unlikely that n-3 fatty acids lower fibrinogen or interact with the fibrinolytic system directly. One prospective secondary prevention trial showed benefits that may have resulted from either an improved hemostatic profile or an antiarrhythmic effect. A similar time course of clinical improvement was noted with reduced rates of cardiac mortality and postoperative thrombosis in Norway during World War II, and this was associated with a drastic dietary alteration involving increased consumption of n-3 fatty acids and reduced consumption of saturated fatty acids. Further work is needed to develop better tools to examine in vivo hemostasis so that the mechanisms and eventual clinical utility of n-3 fatty acids can be elucidated in well- designed clinical trials.

[How do we manage the hemorrhagic risk on hypovitaminosis K and treatments with antivitamin K]

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Ann Fr Anesth Reanim (France) 1998, 17 Suppl 1 p14s-17s

Vitamin K deficiency leads to a deficit in vitamin K-dependent factors, resulting in either hypocoagulability and a decrease in the Quick one-stage prothrombin time expressed as the prothrombin time (PT), or in an increase in INR in patients receiving oral anticoagulation. The anesthesiologist's objective is to bring these values back into the safety range before surgery, i.e., above 50% for PT and below 1.5 for INR. The method to be used will be chosen according to the urgency of the correction. Safety ranges may be reached in 6-12 h following oral or parenteral administration of vitamin K. A 5-mg dose is usually sufficient. If the deficit in vitamin K-dependent factors requires immediate correction, intravenous administration of PPSB should be done. The minimum time during which antivitamin K treatment may be disrupted after surgery depends on both the possibility of restarting oral treatment and the risk of postoperative haemorrhage. During this period, the need for an anticoagulation treatment using heparin should be discussed according to the risk of thrombosis . (3 Refs.)

A double-blind randomized comparison of combined aspirin and ticlopidine therapy versus aspirin or ticlopidine alone on experimental arterial thrombogenesis in humans.

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Blood (United States) Sep 1 1998, 92 (5) p1518-25

No randomized study comparing the effect of combined ticlopidine and aspirin therapy versus each drug alone in reducing poststenting thrombotic complications has been performed. To compare these three antiplatelet regimens versus placebo, we conducted a double-blind randomized study using an ex vivo model of thrombosis . Sixteen healthy male volunteers were assigned to receive for 8 days the following four regimens separated by a 1-month period: aspirin 325 mg/d, ticlopidine 500 mg/d, aspirin 325 mg/d + ticlopidine 500 mg/d, and placebo. At the end of each treatment period, native nonanticoagulated blood was drawn directly from an antecubital vein over collagen- or tissue factor (TF)-coated coverslips positioned in a parallel-plate perfusion chamber at an arterial wall shear rate (2, 600 s-1) for 3 minutes. Thrombus, which formed on collagen in volunteers treated by placebo, were rich in platelets and poor in fibrin. As compared with placebo, aspirin and ticlopidine alone reduced platelet thrombus formation by only 29% and 15%, respectively ($P > .2$). In contrast, platelet thrombus formation was blocked by more than 90% in volunteers treated by aspirin + ticlopidine ($P < .01$ v placebo or each treatment alone). Furthermore, the effect of the drug combination therapy was significantly larger than the sum of the two active treatments ($P < .05$). Thrombus, which formed on TF-coated coverslips in volunteers treated by placebo, were rich in fibrin and platelets. Neither of the three antiplatelet treatments significantly inhibited fibrin deposition and platelet thrombus formation on this surface ($P > .2$). Thus, the present study shows that combined aspirin and ticlopidine therapy dramatically potentiates the antithrombotic effect of each drug alone, but that the antithrombotic effect of the combined treatment depends on the nature of the thrombogenic surface. Copyright 1998 by The American Society of Hematology.

The use of aspirin in polycythaemia vera and primary thrombocythaemia.

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Blood Rev (Scotland) Mar 1998, 12 (1) p12-22

In polycythaemia vera (PV; polycythaemia rubra vera, primary proliferative polycythaemia) and primary thrombocythaemia (PT; essential thrombocythaemia), occlusive complications in the microvasculature and larger vessels are a significant cause of morbidity and mortality. Central to the pathogenesis of these complications are the quantitative and qualitative platelet changes present in these myeloproliferative disorders. Aspirin irreversibly inactivates cyclo-oxygenase in platelets. This leads to a reduced production of platelet thromboxane A2 which has vasoconstricting and platelet aggregatory properties. In haematologically normal individuals, aspirin has been shown to reduce thrombo-embolic complications in populations at risk of these events. In PV and PT, aspirin has been shown to specifically eliminate the micro-circulatory and vasomotor manifestations and there is some evidence of a reduction in larger vessel occlusion. Low-dose aspirin has been shown to substantially reduce the raised thromboxane A2 production of platelets in PV and PT patients. The incidence of haemorrhagic side-effects of aspirin are minimized by the use of low doses. Haemorrhagic events are particularly found in patients with platelet counts > 1000 x 10(9)/l and these events are enhanced by aspirin therapy in these patients. Aspirin should be used with caution in patients with dyspeptic symptoms or a

history of peptic ulceration or bronchospasm. Precise PCV control (< 0.45) and cytoreduction (platelets < 400 x 10(9)/l) should be used in patients with PV to minimize the vascular occlusion risk but routine cytoreduction is proposed only for those at particular risk of vascular occlusion in PT. In the acute presentation of patients with vascular occlusion, cytoreduction and an aspirin dose of 300 mg a day is proposed, reducing to 75 mg a day with the control of symptoms and signs, while 75 mg a day may play a role as prophylactic therapy in the prevention of thrombosis . However, there are no prospective studies in PT to demonstrate the benefit/risk profile and to confirm these recommendations, while a randomized prospective placebo-controlled study of low-dose aspirin in PV has only recently been initiated. (86 Refs.)

[Thrombosis and coronary disease: neutrophils, nitric oxide and aspirin]

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Rev Esp Cardiol (Spain) Mar 1998, 51 (3) p171-7

In recent years, relevant changes have occurred in the knowledge of the cellular mechanisms regulating platelet aggregation and adhesion to the endothelial surface. In particular, major aspects of the interactions between platelets and endothelial cells and neutrophils have been clarified. These interactions involve not only thrombosis -promoting or thrombosis -inhibiting properties but also several aspects of the regulation of vascular function. A new concept has progressively emerged showing thrombosis as a multicellular event in which cell-to cell interactions between platelets, neutrophils, and endothelium regulate the size of a growing thrombus. In brief, there is consistent evidence showing that two vasodilating mediators produced by endothelial cells and neutrophils (nitric oxide and prostacyclin) have antiaggregating platelet effects. Platelet activation is particularly relevant in myocardial ischemia, and several pharmacological strategies have been devised to prevent intravascular platelet activation. Aspirin remains a keystone of these preventive and damage-limiting strategies. Current knowledge maintains that low doses of aspirin decrease in vivo platelet aggregation by a selective inhibitory effect on thromboxane A2 production by platelets with maintenance of prostacyclin production by the endothelium. We have recently focussed our research on the basis that the antiaggregating effect of aspirin could be explained not only by the above-mentioned effects on thromboxane A2 synthesis, but also through its action on neutrophils. Our in vitro and ex vivo studies have demonstrated that neutrophils enhance the antiaggregating effects of acetylsalicilic acid on platelets. We have shown that acetylsalicilic acid stimulates nitric oxide production on neutrophils inhibiting the aggregating effects of thrombin, ADP or epinephrine on platelets. the role of the neutrophils in ischemic events enhancing the tissue damage through the release of several proteases, reactive oxygen species and tumor necrosis factor-alpha has been extensively demonstrated. In an experimental model of acute ischemia/reperfusion in rabbits, we have shown that acetylsalicilic acid is able to enhance the nitric oxide production by neutrophils providing a potential mechanism for the beneficial action of aspirin in the myocardial infarction. Further research is needed to assess the mechanisms of the action of aspirin during the thrombotic phenomena and its effects on the different types of cells that compound the microvascular environment. (42 Refs.)

Prophylaxis for deep vein thrombosis with aspirin or low molecular weight dextran in Korean patients undergoing total hip replacement. A randomized controlled trial.

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Int Orthop (Germany) 1998, 22 (1) p6-10

150 Korean patients undergoing primary uncemented total hip replacement were randomized into 3 treatment groups for deep vein thrombosis (DVT) prophylaxis. Group A(50) were controls; Group B(50) received aspirin 1.2 g daily in 3 divided doses from 2 days before, to 14 days after surgery; Group C(50), received low molecular weight dextran 500 ml, infused intravenously at 50 ml/hour during surgery, and on each of the following 2 days. Contrast venograms were performed prior to surgery and 7-10 days after. The incidence of DVT was 20% in the control group, 12% in the aspirin group ($p < 0.1$ vs control), and 6% in the dextran group ($p < 0.05$ vs control). In patients developing DVT, the ratio of proximal to distal thrombi was increased in the control group as compared to treated groups (4:1 in the control group vs 1.5:1 in the treated groups). Both aspirin and dextran were well tolerated. Obesity ($p < 0.05$) and long-term administration of steroids ($p < 0.05$) were risk factors for deep vein thrombosis which reached statistical significance in the control group. Intraoperative venograms performed on 10 patients, showed that hip flexion (mean 40.4 degrees) plus adduction (mean 11.5 degrees) plus internal rotation (mean 81.5 degrees), resulted in severe twisting or kinking of the femoral vein with stagnation of blood flow. Low molecular weight dextran significantly reduce the incidence of deep venous thrombosis and aspirin, though less effective, had a similar effect.

Effect of supplementation with different doses of DHA on the levels of circulating DHA as non-esterified fatty acid in subjects of Asian Indian background.

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J Lipid Res (United States) Feb 1998, 39 (2) p286-92

There is evidence to indicate that the high rates of coronary heart disease and myocardial infarction amongst Indians of Asian descent may be partly related to circulating nonesterified fatty acids (NEFA). As docosahexaenoic acid (DHA,22:6n-3) in NEFA form has been found to exhibit anti-platelet aggregatory and anti-arrhythmic potential in vitro, the effect of supplementary DHA was examined in healthy subjects of Asian Indian background. Furthermore, time- and dose-dependent changes in absolute levels of DHA as NEFA or phospholipid (PL) were compared. The subjects consumed 8 capsules daily of placebo (DHA-free) or low DHA (0.75 g/day)or high DHA (1.50 g/day) over 6 wks. Fasting blood samples were drawn at days 0, 21, and 42 for analysis of serum lipid/lipoprotein composition. No significant effect of DHA supplementation on the levels of serum lipid/lipoproteins (including Lp[a]) or blood pressure was found. However, the DHA level in serum phospholipid rose by 167% overall with low-dose supplementation (from 2.4-6.4 mol%) but only by an additional 23% upon doubling the dose from 0.75 g to 1.50 g/day. Furthermore, after 6 weeks of supplementation with 0.75 g or 1.5 g DHA/day, absolute concentrations of DHA as PL were not significantly different from the corresponding 3-week values. Interestingly, the absolute concentrations of serum DHA as NEFA showed a marked rise with low-dose supplementation (by 212% overall, from 2.4 to 7.5 microM) and a further 70% rise (to 12.7 microM) upon doubling the supplementation from 0.75 to 1.50 g/day. As well, the 6-week concentrations (DHA-NEFA) were significantly different than the corresponding 3-week values at both dose levels. Elevation of circulating DHA-NEFA levels via DHA supplementation, as shown herein, to concentrations that exhibit anti-thrombotic and anti-arrhythmic potential in vitro needs to be extended to trials where clinical end-points are determined.

Hyperhomocysteinemia and venous thrombosis: A meta-analysis

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Thrombosis and Haemostasis (Germany), 1998, 80/6 (874-877)

Hyperhomocysteinemia is an established risk factor for atherosclerosis and vascular disease. Until the early nineties the relationship with venous thrombosis was controversial. At this mnoment ten case-control studies on venous thrombosis are published, We performed a meta-analysis of these reports. We performed a MEDLINE-search from 1984 through June 1997 on the keywords 'homocysteine' or 'hyperhomocysteinemia' and 'venous thrombosis ', which yielded ten eligible case-control studies. We found a pooled estimate of the odds ratio of 2.5 (95% CI 1.8-3.5) for a fasting plasma homocysteine concentration above the 95th percentile or mean plus two standard deviations calculated from the distribution of the respective control groups. For the post-methionine increase in homocysteine concentration we found a pooled estimate of 2.6 (95% CI 1.6-4.4). These data from case-control studies support hyperhomocysteinemia as a risk factor for venous thrombosis . Further research should focus on the pathophysiology of this relationship and on the clinical effects of reducing homocysteine levels by vitamin supplementation.

Effect of breakfast fat content on glucose tolerance and risk factors of atherosclerosis and thrombosis

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Twenty-four middle-aged healthy men were given a low-fat high-carbohydrate (5.5 g fat; L), or a moderately-fatty, (25.7 g fat; M) breakfast of similar energy contents for 28 d. Other meals were under less control. An oral glucose tolerance test (OGTT) was given at 09.00 hours on day 1 before treatment allocation and at 13.30 hours on day 29. There were no significant treatment differences in fasting serum values, either on day 1 or at the termination of treatments on day 29. The following was observed on day 29: (1) the M breakfast led to higher OGTT C-peptide responses and higher areas under the curves (AUC) of OGTT serum glucose and insulin responses compared with the OGTT responses to the L breakfast ($P < 0\ 05$); (2) treatment M failed to prevent OGTT glycosuria, eliminated with treatment L; (3) serum non-esterified fatty acid (NEFA) AUC was 59% lower with treatment L than with treatment M, between 09.00 and 13.20 hours ($P < 0.0001$), and lower with treatment L than with treatment M during the OGTT ($P = 0.005$); (4) serum triacylglycerol (TAG) concentrations were similar for both treatments, especially during the morning, but their origins were different during the afternoon OGTT when the Svedberg flotation unit 20-400 lipid fraction was higher with

treatment L than with treatment M (P = 0.016); plasma apolipoprotein B-48 level with treatment M was not significantly greater than that with treatment L (P = 0.086); (5) plasma tissue plasminogen-activator activity increased after breakfast with treatment L (P = 0.0008), but not with treatment M (P = 0.80). Waist:hip circumference was positively correlated with serum insulin and glucose AUC and with fasting LDL-cholesterol. Waist:hip circumference and serum TAG and insulin AUC were correlated with factors of thrombus formation; and the OGTT NEFA and glucose AUC were correlated. A small difference in fat intake at breakfast has a large influence on circulating diurnal NEFA concentration, which it is concluded influences adversely glucose tolerance up to 6 h later.

High prevalence of hyperhomocysteinemia in patients with inflammatory bowel disease: A pathogenic link with thromboembolic complications?

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Thrombosis and Haemostasis (Germany), 1998, 80/4 (542-545)

Background and Aims. Why patients with inflammatory bowel disease are at increased risk for thrombosis is unknown. Since they may have impaired absorption of vitamins that regulate the metabolism of homocysteine, we tested the hypothesis that they have hyperhomocysteinemia, an established risk factor for arterial and venous thrombosis .

Methods. The concentrations of total homocysteine (tHcy), folate and cobalamin were measured in blood samples from 61 consecutive patients with inflammatory bowel disease and 183 age- and sex-matched healthy controls.

Results. The mean (plus or minus S.D.) concentration of plasma tHcy was higher in patients (12.2 plus or minus 7.7 micromol/l) than in controls (10.5 plus or minus 4.6, p = 0.045). Eight patients (13%) had concentrations of tHcy higher than the 95th percentile of distribution among controls, as compared with 9 healthy controls (5%, p = 0.04). The prevalence of folate deficiency was higher in patients (15%) than in controls (5%, p = 0.02). Oral administration of folate, cobalamin and pyridoxine to 15 patients for 30 days decreased their mean tHcy levels from 20.3 plus or minus 9.9 to 9.5 plus or minus 3.4 (p < 0.001).

Conclusions. In patients with inflammatory bowel disease there is an increased prevalence of hyperhomocysteinemia, which can be corrected by the administration of folate, cobalamin and pyridoxine. The high prevalence of hyperhomocysteinemia may account for the thrombotic risk of IBD patients; whether or not its correction will decrease the thrombotic risk should be tested in properly designed clinical trials.

Health aspects of fish and n-3 polyunsaturated fatty acids from plant and marine origin

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An expert workshop reviewed the health effects of n-3 polyunsaturated fatty acids (PUFA), and came to the following conclusions. 1. Consumption of fish may reduce the risk of coronary heart disease (CHD). People at risk for CHD are therefore advised to eat fish once a week. The n-3 PUFA in fish are probably the active agents. People who do not eat fish should consider obtaining 200 mg of very long chain n-3 PUFA daily from other sources. 2. Marine n-3 PUFA somewhat alleviate the symptoms of rheumatoid arthritis. 3. There is incomplete but growing evidence that consumption of the plant n-3 PUFA, alpha-linolenic acid, reduces the risk of CHD. An intake of 2 g/d or 1% of energy of alpha-linolenic acid appears prudent. 4. The ratio of total n-3 over n-6 PUFA (linoleic acid) is not useful for characterising foods or diets because plant and marine n-3 PUFA show different effects, and because a decrease in n-6 PUFA intake does not produce the same effects as an increase in n-3 PUFA intake. Separate recommendations for alpha-linolenic acid, marine n-3 PUFA and linoleic acid are preferred. Sponsorship: Supported by a grant from Unilever Research.

Functional food science and the cardiovascular system

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British Journal of Nutrition (United Kingdom), 1998, 80/Suppl. 1

Cardiovascular disease has a multifactorial aetiology, as is illustrated by the existence of numerous risk indicators, many of which can be influenced by dietary means. It should be recalled, however, that only after a cause-and-effect relationship has been established between the disease and a given risk indicator (called a risk factor in that case), can modifying this factor be expected to affect disease morbidity and mortality. In this paper, effects of diet on cardiovascular risk are reviewed, with special emphasis on modification of the plasma lipoprotein profile and of hypertension. In addition, dietary influences on arterial thrombotic processes, immunological interactions, insulin resistance and hyperhomocysteinaemia are discussed. Dietary lipids are able to affect lipoprotein metabolism in a significant way, thereby modifying the risk of cardiovascular disease. However, more research is required concerning the possible interactions between the various dietary fatty acids, and between fatty acids and dietary cholesterol. In addition, more studies are needed with respect to the possible importance of the postprandial state. Although in the aetiology of hypertension the genetic component is definitely stronger than environmental factors, some benefit in terms of the development and coronary complications of atherosclerosis in hypertensive patients can be expected from fatty acids such as alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. This particularly holds for those subjects where the hypertensive mechanism involves the formation of thromboxane A2 and/or alpha1-adrenergic activities. However, large-scale trials are required to test this contention. Certain aspects of blood platelet function, blood coagulability, and fibrinolytic activity are associated with cardiovascular risk, but causality has been insufficiently proven. Nonetheless, well-designed intervention studies should be initiated to further evaluate such promising dietary components as the various n-3 and n-6 fatty acids and their combination, antioxidants, fibre, etc. for their effect on processes participating in arterial thrombus formation. Long-chain polyenes of the n-3 family and antioxidants can modify the activity of immunocompetent cells, but we are at an early stage of examining the role of immune function on the development of atherosclerotic plaques. Actually, there is little, if any, evidence that dietary modulation of immune system responses of cells participating in atherogenesis exerts beneficial effects. Although it seems feasible to modulate insulin sensitivity and subsequent cardiovascular risk factors by decreasing the total amount of dietary fat and increasing the proportion of polyunsaturated fatty acids, additional studies on the efficacy of specific fatty acids, dietary fibre, and low-energy diets, as well as on the mechanisms involved are required to understand the real function of these dietary components. Finally, dietary supplements containing folate and vitamins B6 and/or B12 should be tested for their potential to reduce cardiovascular risk by lowering the plasma level of homocysteine.

Vitamin supplementation reduces blood homocysteine levels: A controlled trial in patients with venous thrombosis and healthy volunteers

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Arteriosclerosis, Thrombosis, and Vascular Biology (United States), 1998, 18/3 (356-361)

Hyperhomocysteinemia is a risk factor for atherosclerosis and thrombosis and is inversely related to plasma folate and vitamin B12 levels. We assessed the effects of vitamin supplementation on plasma homocysteine levels in 89 patients with a history of recurrent venous thrombosis and 227 healthy volunteers. Patients and hyperhomocysteinemic (homocysteine level >16 micromol/L) volunteers were randomized to placebo or high-dose multivitamin supplements containing 5 mg folic acid, 0.4 mg hydroxycobalamin, and 50 mg pyridoxine. A subgroup of volunteers without hyperhomocysteinemia was also randomized into three additional regimens of 5 mg folic acid, 0.5 mg folic acid, or 0.4 mg hydroxycobalamin. Before and after the intervention period, blood samples were taken for measurements of homocysteine, folate, cobalamin, and pyridoxal-5'-phosphate levels. Supplementation with high-dose multivitamin preparations normalized plasma homocysteine levels (less than or equal to 16micromol/L) in 26 of 30 individuals compared with 7 of 30 in the placebo group. Also in normohomocysteinemic subjects, multivitamin supplementation strongly reduced homocysteine levels (median reduction, 30%; range, -22% to 55%). In this subgroup the effect of folic acid alone was similar to that of multivitamin: median reduction, 26%; range, -2% to 52% for 5 mg folic acid and 25%; range, -54% to 40% for 0.5 mg folic acid. Cobalamin supplementation had only a slight effect on homocysteine lowering (median reduction, 10%; range, -21% to 41%). Our study shows that combined vitamin supplementation reduces homocysteine levels effectively in patients with venous thrombosis and in healthy volunteers, either with or without hyperhomocysteinemia. Even supplementation with 0.5 mg of folic acid led to a substantial reduction of blood homocysteine levels.

Homocysteine and vascular diseases

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Hematologie (France), 1998, 4/1 (7-16)

Homocysteine is metabolized through 2 pathways: transsulfuration leading to the formation of cystathionine via cystathionine beta synthase (CbetaS) and its co-factor, pyridoxal 5' phosphate (vitamin B6); remethylation forming methionine via methionine synthase and its coenzyme methylcobalamin, the methyl donor being methyltetrahydrofolate (methylTHF) derived from the reduction of methylene THF via methylenetetrahydrofolate reductase (MTHFR). The increase of homocysteine is an independent risk factor for vascular diseases; indeed hyperhomocysteinemia is toxic for the endothelial cell. The increase of homocysteine is due - to genetic factors: CbetaS or MTHFR deficiency, defective synthesis of active forms of cobalamins - nutritional factors such as folate, vitamin B12 or B6 deficiencies; - some diseases mainly chronic renal insufficiency. In congenital diseases associated with severe hyperhomocysteinemia and huge homocystinuria, the vascular lesion is characterized by precocious atherosclerosis associated to arterial and venous thromboembolism. Besides, numerous epidemiological studies have shown the relationship between moderate hyperhomocysteinemia and the occurrence of vascular diseases, cerebral, coronary, peripheral artery diseases, venous thrombosis . In addition, hyperhomocysteinemia is a predictive risk factor of vascular diseases or even of mortality. There is a relation between plasma homocysteine levels and folate, vitamin B6 and B12 levels from one part, and plasma homocysteine levels and a mutation on the gene of MTHFR C677 right arrow T, which in an homozygous state, usually induces an increase of plasma homocysteine levels. Folic acid alone or in association with vitamin B12 and B6 decreases and often normalizes homocysteine levels. Folic acid supplementation could be an effective treatment, inexpensive and not toxic for the prevention of some vascular diseases.

Coffee consumption in hypertensive men in older middle-age and the risk of stroke: the Honolulu Heart Program.

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J Clin Epidemiol (England) Jun 1998, 51 (6) p487-94

OBJECTIVE: To examine the association between coffee consumption and the development of stroke in men at high risk for cardiovascular disease.

METHODS: Coffee intake was observed from 1965 to 1968 in a cohort of men enrolled in the Honolulu Heart Program with follow-up for incident stroke over a 25-year period. Subjects were 499 hypertensive men (having systolic or diastolic blood pressures at or above 140 and 90 mm Hg, respectively) in older middle-age (55 to 68 years) when follow-up began. Past and current cigarette smokers were excluded from follow-up.

RESULTS: In the course of follow-up, 76 men developed a stroke. After age-adjustment, risk of thromboembolic stroke increased significantly with increases in coffee consumption ($P = 0.002$). No relationships were observed with hemorrhagic stroke. When adjusted for other factors, the risk of thromboembolic stroke was more than doubled for men who consumed three cups of coffee per day as compared to nondrinkers of coffee (RR = 2.1; 95% CI = 1.2-3.7).

CONCLUSIONS: Although in need of further confirmation, consumption of coffee appears to be positively associated with an increased risk of thromboembolic stroke in hypertensive men in older middle-age. Findings suggest that it may be prudent to advise older middle-aged men with hypertension who consume large amounts of coffee to consider reducing their coffee intake.

Lipids and stroke: Neglect of a useful preventive measure?

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Cardiovascular Research (Netherlands), 1998, 40/2 (265-271)

The epidemiological studies linking lipid variables and stroke are reviewed. These studies indicate that serum total cholesterol (TC) levels are associated positively with thrombotic and negatively with haemorrhagic strokes. Relationships for other lipid fractions are not as clearly defined. The results of trials with lipid lowering drugs suggest that only statins effectively reduce the incidence of stroke. Differences between trial results may be due to variation in the extent of reduction of TC levels. Possible underlying mechanisms for benefit and the apparent superiority of statins are also discussed. The reduction in the risk of thrombotic stroke with statins is most evident through meta-analyses ($p<0.001$) and less impressive in individual trials ($p<0.03$). This difference is largely attributable to the small number of events in trials primarily aimed at evaluating ischaemic heart disease (IHD) reduction. This also means that benefit may be limited to those with established IHD. IHD and thrombotic stroke share common risk factors

and patients with one condition are at high risk of developing the other. Therefore, one additional reason for using statins in these patients is that these drugs can effectively prevent IHD-related events including deaths.

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