

ABSTRACTS**Colon Cancer****APPLE PHYTOCHEMICALS AND THEIR HEALTH BENEFITS.**

Evidence suggests that a diet high in fruits and vegetables may decrease the risk of chronic diseases, such as cardiovascular disease and cancer, and phytochemicals including phenolics, flavonoids and carotenoids from fruits and vegetables may play a key role in reducing chronic disease risk. Apples are a widely consumed, rich source of phytochemicals, and epidemiological studies have linked the consumption of apples with reduced risk of some cancers, cardiovascular disease, asthma, and diabetes. In the laboratory, apples have been found to have very strong antioxidant activity, inhibit cancer cell proliferation, decrease lipid oxidation, and lower cholesterol. Apples contain a variety of phytochemicals, including quercetin, catechin, phloridzin and chlorogenic acid, all of which are strong antioxidants. The phytochemical composition of apples varies greatly between different varieties of apples, and there are also small changes in phytochemicals during the maturation and ripening of the fruit. Storage has little to no effect on apple phytochemicals, but processing can greatly affect apple phytochemicals. While extensive research exists, a literature review of the health benefits of apples and their phytochemicals has not been compiled to summarize this work. The purpose of this paper is to review the most recent literature regarding the health benefits of apples and their phytochemicals, phytochemical bioavailability and antioxidant behavior, and the effects of variety, ripening, storage and processing on apple phytochemicals.

Nutr J. 2004 May 12;3(1):5

SHOULD CALCIUM AND VITAMIN D BE ADDED TO THE CURRENT ENRICHMENT PROGRAM FOR CEREAL-GRAIN PRODUCTS?

Mean dietary intakes of calcium and vitamin D in the US adult population are far below the adequate intake (AI) values recommended by the Food and Nutrition Board, Institute of Medicine of the National Academy of Sciences, and thus substantial segments of the American population have inadequate intakes and elevated risks of osteoporosis and colon cancer. The current Code of Federal Regulations, Title 21, sets standards for the optional addition of moderate amounts of calcium and vitamin D in the enrichment of cereal-grain products, a provision that is essentially not used. We propose that the addition of calcium and vitamin D to currently enriched cereal-grain products be mandated in the United States: this would result in an increase in mean daily dietary intakes in the United States of approximately 400 mg Ca and ≥ 50 IU (or possibly >200 IU) vitamin D. The benefits would be a significant reduction in the incidences of osteoporosis and colon cancer over time and overall improvement in health, with little risk and a modest financial cost because of the ability to capitalize on existing technology. We suggest a full scientific review of cereal-grain enrichment with calcium and vitamin D.

Am J Clin Nutr. 2004 Aug;80(2):264-70

EFFECT OF CALCIUM SUPPLEMENTATION ON THE RISK OF LARGE BOWEL POLYPS.

BACKGROUND: Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas. However, few studies have examined the effect of calcium on the risk of different types of colorectal lesions or dietary determinants of this effect. **METHODS:** Our analysis used patients from the Calcium Polyp Prevention Study, a randomized, double-blind, placebo-controlled chemoprevention trial among patients with a recent colorectal adenoma. Nine hundred thirty patients were randomly assigned to calcium carbonate (1200 mg/day) or placebo. Follow-up colonoscopies were conducted approximately 1 and 4 years after the qualifying examination. We used general estimating equation (GEE) and generalized linear regression analyses to compute risk ratios and 95% confidence intervals (CIs) to assess the effect of calcium treatment versus placebo on the risk of hyperplastic polyps, tubular adenomas, and more advanced lesions. Additionally, we used GEE analyses to compare the calcium treatment effects for various types of polyps with that for tubular adenomas. We also examined the interaction between calcium treatment and baseline intake of dietary calcium, fat, and fiber. All P values were obtained using Wald tests based on the corresponding models. All tests of statistical significance were two-sided. **RESULTS:** The calcium risk ratio for hyperplastic polyps was 0.82 (95% CI = 0.67 to 1.00), that for tubular adenomas was 0.89 (95% CI = 0.77 to 1.03), and that for histologically advanced neoplasms was 0.65 (95% CI = 0.46 to 0.93) compared with patients assigned to placebo. There were no statistically significant differences between the risk ratio for tubular adenomas and that for other types of polyps. The

effect of calcium supplementation on adenoma risk was most pronounced among individuals with high dietary intakes of calcium and fiber and with low intake of fat, but the interactions were not statistically significant. **CONCLUSION:** Our results suggest that calcium supplementation may have a more pronounced antineoplastic effect on advanced colorectal lesions than on other types of polyps.

J Natl Cancer Inst. 2004 Jun 16;96(12):921-5

DIETARY CANCER AND PREVENTION USING ANTIMUTAGENS.

Many of the cancers common in the Western world, including colon, prostate and breast cancers, are thought to relate to dietary habits. Of the known risk factors, many will act through increasing the probability of mutation. Recognised dietary mutagens include cooked meat compounds, N-nitroso compounds and fungal toxins, while high meat and saturated fat consumption, increasing rates of obesity, and regular consumption of alcohol and tobacco are all dietary trends that could indirectly enhance the probability of mutation. However, there are significant difficulties in implementing and sustaining major dietary changes necessary to reduce the population's intake of dietary mutagens. Dietary antimutagens may provide a means of slowing progression toward cancer, and be more acceptable to the population. Consideration of genetic mechanisms in cancer development suggest several distinct targets for intervention. Strategies that reduce mutagen uptake may be the most simple intervention, and the one least likely to result in undesirable side effects. Certain (but not all) types of dietary fibres appear to reduce mutation through this mechanism, as may certain probiotics and large planar molecules such as chlorophyllin. Antioxidants have been suggested to scavenge free radicals, and prevent their interactions with cellular DNA. Small molecule dietary antioxidants include ascorbic acid, Vitamin E, glutathione, various polyphenols and carotenoids. We found a statistically significant relationship between colon cancer incidence and soil selenium status across different regions of New Zealand. Additionally, a study of middle-aged men suggested that blood selenium levels lower than 100 ng/ml were inadequate for repair or surveillance of oxidative (and other) DNA damage. We suggest that selenium will be an important antimutagen, at least in New Zealand, possibly through antioxidant effects associated with selenium's role in enzymes associated with endogenous repair of DNA damage. Modulation of xenobiotic metabolizing enzymes is well recognised as cancer-protective, and is a property of various flavonoids and a number of sulfur-containing compounds. Many fruits and vegetables contain compounds that will protect against mutation and cancer by several mechanisms. For example, kiwifruit has antioxidant effects and may also affect DNA repair enzymes. Dietary folate may be a key factor in maintenance of methylation status, while enhanced overall levels of vitamins and minerals may retard the development of genomic instability. The combination of each of these factors could provide a sustainable intervention that might usefully delay the development of cancer in New Zealand and other populations. Although there are a range of potentially antimutagenic fruits, vegetables and cereals available to these populations, current intake is generally below the level necessary to protect from dietary or endogenous mutagens. Dietary supplementation may provide an alternative approach.

Toxicology. 2004 May 20;198(1-3):147-59

DIETARY ANTIOXIDANTS AND HUMAN CANCER.

Epidemiological studies show that a high intake of anti-oxidant-rich foods is inversely related to cancer risk. While animal and cell cultures confirm the anticancer effects of antioxidants, intervention trials to determine their ability to reduce cancer risk have been inconclusive, although selenium and vitamin E reduced the risk of some forms of cancer, including prostate and colon cancer, and carotenoids have been shown to help reduce breast cancer risk. Cancer treatment by radiation and anticancer drugs reduces inherent antioxidants and induces oxidative stress, which increases with disease progression. Vitamins E and C have been shown to ameliorate adverse side effects associated with free radical damage to normal cells in cancer therapy, such as mucositis and fibrosis, and to reduce the recurrence of breast cancer. While clinical studies on the effect of anti-oxidants in modulating cancer treatment are limited in number and size, experimental studies show that antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread, suggesting a potential role for antioxidants as adjuvants in cancer therapy.

Integr Cancer Ther. 2004 Dec;3(4):333-41

PHARMACOLOGICAL EFFECTS OF GREEN TEA ON THE GASTROINTESTINAL SYSTEM.

Green tea is rich in polyphenolic compounds, with catechins as its major component. Studies have shown that catechins possess diverse pharmacological properties that include anti-oxidative, anti-inflammatory, anti-carcinogenic, anti-arteriosclerotic and anti-bacterial effects. In the gastrointestinal tract, green tea was found to activate intracellular antioxidants, inhibit procarcinogen formation, suppress angiogenesis and cancer cell proliferation. Studies on the preventive effect of green tea in esophageal cancer have produced inconsistent results; however, inverse relationships of tea consumption with cancers of the stomach and colon have been widely reported. Green tea is effective to prevent dental caries and reduce cholesterol and lipids absorption in the gastrointestinal tract, thus benefits subjects with cardiovascular disorders. As tea catechins are well absorbed in the gastrointestinal tract and they interact synergistically in their disease-modifying actions, thus drinking unfractionated green

tea is the most simple and beneficial way to prevent gastrointestinal disorders.

Eur J Pharmacol. 2004 Oct 1;500(1-3):177-85

EPIGALLOCATECHIN, A GREEN TEA POLYPHENOL, ATTENUATES MYOCARDIAL ISCHEMIA REPERFUSION INJURY IN RATS.

Epigallocatechin-3-gallate (EGCG) is the most prominent catechin in green tea. EGCG has been shown to modulate numerous molecular targets in the setting of inflammation and cancer. These molecular targets have also been demonstrated to be important participants in reperfusion injury, hence this study examines the effects of EGCG in myocardial reperfusion injury. Male Wistar rats were subjected to myocardial ischemia (30 min) and reperfusion (up to 2 h). Rats were treated with EGCG (10 mg/kg intravenously) or with vehicle at the end of the ischemia period followed by a continuous infusion (EGCG 10 mg/kg/h) during the reperfusion period. In vehicle-treated rats, extensive myocardial injury was associated with tissue neutrophil infiltration as evaluated by myeloperoxidase activity, and elevated levels of plasma creatine phosphokinase. Vehicle-treated rats also demonstrated increased plasma levels of interleukin-6. These events were associated with cytosol degradation of inhibitor kappaB-alpha, activation of IkappaB kinase, phosphorylation of c-Jun, and subsequent activation of nuclear factor-kappaB and activator protein-1 in the infarcted heart. In vivo treatment with EGCG reduced myocardial damage and myeloperoxidase activity. Plasma IL-6 and creatine phosphokinase levels were decreased after EGCG administration. This beneficial effect of EGCG was associated with reduction of nuclear factor-kB and activator protein-1 DNA binding. The results of this study suggest that EGCG is beneficial for the treatment of reperfusion-induced myocardial damage by inhibition of the NF-kappaB and AP-1 pathway.

Mol Med. 2004 Jan-Jun;10(1-6):55-6

ABSTRACTS**Vitamin E****EFFECTS OF VITAMIN E SUPPLEMENTATION ON OXIDATIVE STRESS IN STREPTOZOTOCIN INDUCED DIABETIC RATS: INVESTIGATION OF LIVER AND PLASMA.**

This experimental study was designed to investigate the effects of vitamin E supplementation, especially on lipid peroxidation and antioxidant status elements 3/4 namely, glutathione (GSH), CuZn superoxide dismutase (CuZn SOD), and glutathione peroxidase (GSH Px), both in blood and liver tissues of streptozotocin (STZ) diabetic rats. The extent to which blood can be used to reflect the oxidative stress of the liver is also investigated. In diabetic rats, plasma lipid peroxide values were not significantly different from control, whereas erythrocyte CuZn SOD ($p < 0.01$), GSH Px ($p < 0.001$) activities and plasma vitamin E levels ($p < 0.001$), were significantly more elevated than controls. Vitamin E supplementation caused significant decreases of erythrocyte GSH level ($p < 0.01$) in control rats and of erythrocyte GSH Px activity ($p < 0.05$) in diabetic rats. Liver findings revealed significantly higher lipid peroxide ($p < 0.001$) and vitamin E ($p < 0.01$) levels and lower GSH ($p < 0.001$), CuZn SOD ($p < 0.001$) and GSH Px ($p < 0.01$) levels in diabetic rats. A decreased hepatic lipid peroxide level ($p < 0.01$) and increased vitamin E/lipid peroxide ratio ($p < 0.001$) were observed in vitamin E supplemented, diabetic rats. A vitamin E supplementation level which did not cause any increase in the concentration of the vitamin in the liver or blood, was sufficient to lower lipid peroxidation in the liver. Vitamin E/lipid peroxide ratio is suggested as an appropriate index to evaluate the efficiency of vitamin E activity, independent of tissue lipid values. Further, the antioxidant components GSH, GSH Px and CuZn SOD and the relationships among them, were affected differently in the liver and blood by diabetes or vitamin E supplementation.

Yonsei Med J. 2004 Aug 31;45(4):703-10

LIPID PEROXIDATION IN MEN AFTER DIETARY SUPPLEMENTATION WITH A MIXTURE OF ANTIOXIDANT NUTRIENTS.

Antioxidants and antioxidant enzymes protect living organisms against the attack of reactive oxygen species. An adequate daily intake of the individual antioxidants is therefore important to prevent the cells against oxidative damage. We investigated the effect of a modest dietary supplementation with a mixture of antioxidant nutrients (100 mg vitamin E, 100 mg vitamin C, 6 mg beta-carotene and 50 microg of selenium per day) for 3 months on the plasma antioxidant capacity and indices of oxidative stress. Two groups of middle-age men were selected: group 1 with survivors of myocardial infarction (MI), and group 2 with clinically normal controls. The values of total antioxidant capacity of plasma (FRAP) significantly increased after supplementation with antioxidants in the both groups. Markers of in vivo lipid peroxidation, plasma malondialdehyde (MDA) and conjugated diene (CD) levels significantly decreased in the both supplemented groups. MDA and CD values were significantly higher at baseline in the group of survivors of myocardial infarction when compared with the group of healthy men. The results demonstrate that short-term and modest supplementation with a mixture of antioxidant nutrients improves antioxidative capacity and reduces products of lipid peroxidation in plasma. Since a more pronounced effect was observed within the group of survivors of myocardial infarction, a recommendation of antioxidant supplements seems appropriate for patients with a history of cardiovascular disease.

Bratisl Lek Listy. 2004;105(7-8):277-80

THE ROLE OF METABOLISM IN THE ANTIOXIDANT FUNCTION OF VITAMIN E.

Vitamin E (alpha-tocopherol), the principal chain-breaking antioxidant in biological membranes, prevents toxicant- and carcinogen-induced oxidative damage by trapping reactive oxyradicals. Although alpha-tocopherol antioxidant reactions appear to be not under direct metabolic control, alpha-tocopherol may function through redox cycles, which deliver reducing equivalents for antioxidant reactions and link antioxidant function to cellular metabolism. This review describes the antioxidant chemistry of alpha-tocopherol and evaluates the experimental evidence for the linkage of alpha-tocopherol turnover to cellular metabolism through redox cycles. Numerous in vitro experiments demonstrate antioxidant synergism between alpha-tocopherol and ascorbate, reduced glutathione, NADPH, and cellular electron transport proteins. Nevertheless, evidence that a one-electron redox cycle regenerates alpha-tocopherol from the tocopheroxyl radical is inconclusive. The difficulty of separating tocopheroxyl recycling from direct antioxidant actions of other antioxidants has complicated interpretation of the available data. A two-electron redox cycle involving alpha-tocopherol oxidation to 8 α -substituted tocopherones followed by tocopherone reduction to alpha-tocopherol may occur, but would require enzymatic catalysis in vivo. Metabolism of antioxidant-inactive alpha-tocopheryl esters releases alpha-tocopherol, whereas reductive metabolism of alpha-tocopherylquinone, an alpha-tocopherol oxidation product, yields alpha-tocopherylhydroquinone, which also may provide antioxidant protection.

REGULATION OF SELENOPROTEIN GPX4 EXPRESSION AND ACTIVITY IN HUMAN ENDOTHELIAL CELLS BY FATTY ACIDS, CYTOKINES AND ANTIOXIDANTS.

Phospholipid hydroperoxide glutathione peroxidase (GPx4) is the only antioxidant enzyme known to directly reduce phospholipid hydroperoxides within membranes and lipoproteins, acting in conjunction with alpha-tocopherol to inhibit lipid peroxidation. Peroxidation of lipids has been implicated in a number of pathophysiological processes, including inflammation and atherogenesis. We investigated the relative positive and negative effects of specific polyunsaturated fatty acids (PUFAs) and inflammatory cytokines on the activity and gene expression of the selenium-dependant redox enzyme GPx4. In human umbilical vein endothelial cells (HUVEC), GPx4 mRNA levels and activity were increased optimally by 114 nM selenium (as sodium selenite). Docosahexaenoic acid (DHA) and conjugated linoleic acid (CLA) further increased mRNA levels whereas arachidonic acid (ARA) had no effect; enzyme activity was decreased by DHA, was unaffected by CLA or was increased by ARA. GPx4 protein levels increased with selenium, ARA and DHA addition but not with CLA. Interleukin-1beta (IL-1beta) increased GPx4 mRNA, protein and activity whereas TNFalpha at 1 ng/ml increased activity while at 3 ng/ml it reduced activity and mRNA. Conversely, alpha-tocopherol reduced mRNA levels without affecting activity. These results indicate that lipids, cytokines and antioxidants modulate GPx4 in a complex manner that in the presence of adequate selenium, may favour protection against potentially proatherogenic processes.

Atherosclerosis. 2003 Nov;171(1):57-65

SUPPLEMENTATION OF DIETS WITH ALPHA-TOCOPHEROL REDUCES SERUM CONCENTRATIONS OF GAMMA- AND DELTA-TOCOPHEROL IN HUMANS.

Despite promising evidence from in vitro experiments and observational studies, supplementation of diets with alpha-tocopherol has not reduced the risk of cardiovascular disease and cancer in most large-scale clinical trials. One plausible explanation is that the potential health benefits of alpha-tocopherol supplements are offset by deleterious changes in the bioavailability and/or bioactivity of other nutrients. We studied the effects of supplementing diets with RRR-alpha-tocopheryl acetate (400 IU/d) on serum concentrations of gamma- and delta-tocopherol in a randomized, placebo-controlled trial in 184 adult nonsmokers. Outcomes were changes in serum concentrations of gamma- and delta-tocopherol from baseline to the end of the 2-mo experimental period. Compared with placebo, supplementation with alpha-tocopherol reduced serum gamma-tocopherol concentrations by a median change of 58% [95% CI = (51%, 66%), $P < 0.0001$], and reduced the number of individuals with detectable delta-tocopherol concentrations ($P < 0.0001$). Consistent with trial results were the results from baseline cross-sectional analyses, in which prior vitamin E supplement users had significantly lower serum gamma-tocopherol than nonusers. In view of the potential benefits of gamma- and delta-tocopherol, the efficacy of alpha-tocopherol supplementation may be reduced due to decreases in serum gamma- and delta-tocopherol levels. Additional research is clearly warranted.

J Nutr. 2003 Oct;133(10):3137-4

ABSTRACTS

Folic acid

A ROLE FOR SUPPLEMENTS IN OPTIMIZING HEALTH: THE METABOLIC TUNE-UP.

An optimum intake of micronutrients and metabolites, which varies with age and genetic constitution, would tune up metabolism and give a marked increase in health, particularly for the poor, young, obese, and elderly, at little cost. (1) DNA damage. Deficiency of vitamins B-12, folic acid, B-6, C or E, or iron or zinc appears to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions or both. Half of the population may be deficient in at least one of these micronutrients. (2) The Km concept. Approximately 50 different human genetic diseases that are due to a poorer binding affinity (Km) of the mutant enzyme for its coenzyme can be remedied by feeding high-dose B vitamins, which raise levels of the corresponding coenzyme. Many polymorphisms also result in a lowered affinity of enzyme for coenzyme. (3) Mitochondrial oxidative decay. This decay, which is a major contributor to aging, can be ameliorated by feeding old rats the normal mitochondrial metabolites acetyl carnitine and lipoic acid at high levels. Many common micronutrient deficiencies, such as iron or biotin, cause mitochondrial decay with oxidant leakage leading to accelerated aging and neural decay.

Arch Biochem Biophys. 2004 Mar 1;423(1):227-34

HOMOCYSTEINE AND REACTIVE OXYGEN SPECIES IN METABOLIC SYNDROME, TYPE 2 DIABETES MELLITUS, AND ATHEROSCLEROPATHY: THE PLEIOTROPIC EFFECTS OF FOLATE SUPPLEMENTATION.

Homocysteine has emerged as a novel independent marker of risk for the development of cardiovascular disease over the past three decades. Additionally, there is a graded mortality risk associated with an elevated fasting plasma total homocysteine (tHcy). Metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) are now considered to be a strong coronary heart disease (CHD) risk enhancer and a CHD risk equivalent respectively. Hyperhomocysteinemia (HHcy) in patients with MS and T2DM would be expected to share a similar prevalence to the general population of five to seven percent and of even greater importance is: Declining glomerular filtration and overt diabetic nephropathy is a major determinant of tHcy elevation in MS and T2DM. There are multiple metabolic toxicities resulting in an excess of reactive oxygen species associated with MS, T2DM, and the accelerated atherosclerosis (atherosclerosis). HHcy is associated with an increased risk of cardiovascular disease, and its individual role and how it interacts with the other multiple toxicities are presented. The water-soluble B vitamins (especially folate and cobalamin-vitamin B12) have been shown to lower HHcy. The absence of the cystathionine beta synthase enzyme in human vascular cells contributes to the importance of a dual role of folic acid in lowering tHcy through remethylation, as well as, its action of being an electron and hydrogen donor to the essential cofactor tetrahydrobiopterin. This folate shuttle facilitates the important recoupling of the uncoupled endothelial nitric oxide synthase enzyme reaction and may restore the synthesis of the omnipotent endothelial nitric oxide to the vasculature.

Nutr J. 2004 May 10;3(1):4

INFLAMMATION AND ENDOTHELIAL DYSFUNCTION: INTIMATE COMPANIONS IN THE PATHOGENESIS OF VASCULAR DISEASE?

There is increasing evidence to implicate inflammation as an important precursor of endothelial dysfunction. This mechanistic link is apparent across the entire spectrum of inflammatory status, i.e. endothelial function is apparent following acute infection, and in subjects with chronic high-grade inflammation and, perhaps most importantly, persistent low-grade inflammation. The recognition of this relationship has present therapeutic ramifications, but also requires that future longitudinal studies determining the predictive ability of endothelial function measures for vascular events should incorporate markers of inflammation as potential confounders. In this issue of Clinical Science, Fichtlscherer and co-workers describe a link between endothelial function and sPLA(2) (secretory non-pancreatic type II phospholipase A(2)) serum activity.

Clin Sci (Lond). 2004 May;106(5):443-5

AGE-ASSOCIATED CHANGES IN THE METABOLISM OF VITAMIN B(12) AND FOLIC ACID: PREVALENCE, AETIOPATHOGENESIS AND PATHOPHYSIOLOGICAL CONSEQUENCES.

The increasing number of older people is characteristic for most industrialised nations and implicates the known psychosocial and economic consequences. Therefore, an optimal nutrient supply that promotes continuing mental and physical well-being is particularly important. In this respect, vitamin B(12) and folic acid play a major role, since deficiency of both vitamins is

associated with the pathogenesis of different diseases such as declining neurocognitive function and atherosclerotic lesions. Vitamin B(12) and folic acid act as coenzymes and show a close molecular interaction on the basis of the homocysteine metabolism. In addition to the serum concentrations of the vitamins, the metabolites homocysteine and methylmalonic acid are sensitive markers of cobalamin and folate status. Depending on the used marker, 3-60% of the elderly are classified as vitamin B(12) deficient and about 29% as folate deficient. Predominantly, this high prevalence of poor cobalamin status is caused by the increasing prevalence of atrophic gastritis type B, which occurs with a frequency of approximately 20-50% in elderly subjects. Atrophic gastritis results in declining gastric acid and pepsinogen secretion, and hence decreasing intestinal digestion and absorption of both B vitamins. This is the reason why an insufficient vitamin B(12) status in the elderly is rarely due to low dietary intake. In contrast, folic acid intake among elderly subjects is generally well below the recommended dietary reference values. Even moderately increased homocysteine levels or poor folate and vitamin B(12) status are associated with vascular disease and neurocognitive disorders. Results of a meta-analysis of prospective studies revealed that a 25% lower homocysteine level (about 3 micromol/L) was associated with an 11% lower ischemic heart disease risk and 19% lower stroke risk. It is still discussed, whether hyperhomocysteinemia is causally related to vascular disease or whether it is a consequence of atherosclerosis. Estimated risk reduction is based on cohort studies, not on clinical trials. Homocysteine initiates different proatherogenic mechanisms such as the formation of reactive oxygen species and an enhanced fibrin synthesis. Supplementation of folic acid (0.5-5 mg/d) reduces the homocysteine concentration by 25%. Additional vitamin B(12) (0.5 mg/d) induces further reduction by 7%. In secondary prevention, supplementation already led to clinical improvements (reduction of restenosis rate and plaques). Depression, dementia, and mental impairment are often associated with folate and vitamin B(12) deficiency. The biochemical reason of this finding may be the importance of folic acid and vitamin B(12) for the transmethylation of neuroactive substances (myelin, neurotransmitters) which is impaired in vitamin deficiency ("hypomethylation hypothesis"). In recent years, there is increasing evidence for a role of folic acid in cancer prevention. As a molecular mechanism of a preventive effect of folic acid the hypomethylation of certain DNA sections in folate deficiency has been suggested. Since folate and vitamin B(12) intake and status are mostly insufficient in elderly subjects, a supplementation can generally be recommended.

Z Gerontol Geriatr. 2004 Apr;37(2):109-35

ENDOTHELIAL FUNCTION IN POST-MENOPAUSAL WOMEN: EFFECT OF FOLIC ACID SUPPLEMENTATION.

BACKGROUND: Higher than normal homocysteine levels are associated with an increased incidence of adverse cardiovascular events in post-menopausal women, perhaps via hyperhomocysteinemia-induced vascular endothelial damage. Because folic acid supplementation reduces homocysteine levels, we attempted to evaluate whether folic acid supplementation may affect endothelial function in post-menopausal women. **METHODS:** Brachial artery flow-mediated dilatation (endothelium-dependent) and nitroglycerin-induced dilatation (endothelium-independent) before and after a methionine load were analysed in 15 healthy post-menopausal women. Plasma levels of folate, homocysteine, glucose, insulin and lipids were measured, as was blood pressure. All studies were repeated after 1 month supplementation with 7.5 mg/day of folic acid. **RESULTS:** After folate, endothelial function rose 37% over pre-folic acid supplementation value ($P < 0.001$), and flow-mediated dilation before folic acid was reduced by 62% subsequent to methionine loading ($P < 0.0001$); this reduction was still present after folic acid, but was only 19% ($P < 0.001$). Nitroglycerin-induced dilatation did not change in response to methionine loading before or after folic acid supplementation. Among the other cardiovascular risk factors studied, only high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol showed significant changes after folic acid supplementation, with a 6% increase ($P < 0.03$) and a 9% decrease ($P < 0.03$) respectively. **CONCLUSIONS:** Although preliminary, these results indicate that folic acid supplementation may improve endothelial function and lipid profile in post-menopausal women, thus contributing to reduce their cardiovascular risk.

Hum Reprod. 2004 Apr;19(4):1031-5. Epub 2004 Mar 11

HOMOCYSTEINE AND THE BRAIN IN MIDADULT LIFE: EVIDENCE FOR AN INCREASED RISK OF LEUKOARAIOSIS IN MEN.

BACKGROUND: High serum homocysteine (HCY) levels have been associated with thromboembolic cerebrovascular disease, but their relationship to microvascular disease is uncertain. Homocysteine also has a direct neurotoxic effect and has been linked to brain atrophy and an increased risk of Alzheimer disease. **OBJECTIVE:** To examine the relationship of HCY levels to brain and cognitive measures in a healthy community sample. **DESIGN:** Cross-sectional study. **SETTING:** Individuals residing in Canberra and Queanbeyan, Australia, who were participating in the longitudinal PATH Through Life Project. **PARTICIPANTS:** Individuals aged 60 to 64 years selected randomly from the community, 196 men and 189 women. **MAIN OUTCOME MEASURES:** Regression coefficients with HCY level as the putative determinant and various magnetic resonance imaging measures (brain atrophy index, ventricle-brain ratios, volume of periventricular and deep white matter hyperintensities) and cognitive measures (information processing speed, verbal memory, fine motor speed) as dependent measures. **RESULTS:** Homocysteine levels did not have a significant relationship with brain atrophy index or ventricle-brain ratios. High HCY levels were related to increased deep white matter hyperintensities but not periventricular white matter hyperintensities, after correcting for levels of folate, vitamin B(12), creatinine, and thyrotropin; hypertension; smoking; and diabetes, the relationship being significant only in men. Homocysteine levels were related to impairment in verbal memory and fine motor speed but not after the previously mentioned correction. **CONCLUSIONS:** Total HCY level is independently related to leukoaraiosis in middle-aged men, and this

may be functionally relevant in the form of mild cognitive impairment. The remediation of hyperhomocysteinemia should begin early in life if its deleterious effects on the brain are to be prevented.

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