

ABSTRACTS**Life Extension Mix****VEGETABLES, FRUITS AND PHYTOESTROGENS IN THE PREVENTION OF DISEASES.**

The intake of 400-600 g/d of fruits and vegetables is associated with reduced incidence of many common forms of cancer, and diets rich in plant foods are also associated with a reduced risk of heart disease and many chronic diseases of ageing. These foods contain phytochemicals that have anti-cancer and anti-inflammatory properties which confer many health benefits. Many phytochemicals are colourful, and recommending a wide array of colourful fruits and vegetables is an easy way to communicate increased diversity of intake to the consumer. For example, red foods contain lycopene, the pigment in tomatoes, which is localized in the prostate gland and may be involved in maintaining prostate health, and which has also been linked with a decreased risk of cardiovascular disease. Green foods, including broccoli, brussels sprouts, and kale, contain glucosinolates which have also been associated with a decreased risk of cancer. Garlic and other white-green foods in the onion family contain allyl sulphides which may inhibit cancer cell growth. Other bioactive substances in green tea and soybeans have health benefits as well. Consumers are advised to ingest one serving of each of the seven colour groups daily, putting this recommendation within the United States National Cancer Institute and American Institute for Cancer Research guidelines of five to nine servings per day. Grouping plant foods by colour provides simplification, but it is also important as a method to help consumers make wise food choices and promote health.

J Postgrad Med. 2004 Apr-Jun;50(2):145-9

INDUCTION OF PHASE II DETOXIFICATION ENZYMES IN RATS BY PLANT-DERIVED ISOTHIOCYANATES: COMPARISON OF ALLYL ISOTHIOCYANATE WITH SULFORAPHANE AND RELATED COMPOUNDS.

Plants of the family Brassicaceae contain high levels of glucosinolates. The latter compounds are degraded to isothiocyanates, some of which have been shown to be potent inducers of phase II detoxification enzymes in vitro. In the present study, the ability of six plant-derived isothiocyanates (allyl isothiocyanate, isoberberin, erucin, sulforaphane, isoberberin, and cheirolin) to increase tissue levels of the phase II detoxification enzymes quinone reductase (QR) and glutathione S-transferase (GST) in a variety of rat tissues has been compared. At the low dose level employed (40 micromol/kg/day), cheirolin was without effect in any tissue. All of the other isothiocyanates, however, increased GST and QR activities in the duodenum, forestomach, and/or the urinary bladder of the animals, with the greatest effects being seen in the urinary bladder. With the exception of cheirolin, little difference was observed in the inductive activity of the various isothiocyanates. Phase II enzymes are known to protect against chemical carcinogenesis, and the selectivity of isothiocyanates in inducing such enzymes in the bladder is of interest in view of recent epidemiological studies showing a decreased incidence of cancer of this organ in individuals with a high dietary intake of Brassica vegetables.

J Agric Food Chem. 2004 Apr 7;52(7):1867-71

CONSEQUENCES OF MODERATE HYPERHOMOCYSTEINEMIA IN THE INTERNAL MEDICINE.

Homocysteine is an intermediate product in the methionine metabolism, which is catalysed by several enzymes with B2, B6, B12 vitamins and folic acid as cofactors. Moderate hyperhomocysteinemia, defined as total homocysteine concentration between 12 to 30 micromol/l, represents an independent risk factor for heart disease, vascular brain disease, phlebotrombosis and thromboembolic complications. It is related to placental abruptions, spina bifida and some neuropsychiatric disorders. Hyperhomocysteinemia is a metabolic syndrome based on interaction between genetic factors (most frequently 677C/T polymorphism of methylentetrahydrofolate reductase), diseases and demographic factors (smoking, aging, hormonal and nutritional factors). Moderate hyperhomocysteinemia occurs in about 20 to 30% of patients with clinical complications of atherosclerosis. Prospective and genetic studies have shown, that moderate hyperhomocysteinemia in healthy persons is only a weak predictor of cardiovascular diseases. Contrary to it, in patients with ischaemic heart disease, renal failure or diabetes mellitus and in thromboembolic disease, hyperhomocysteinemia represents a strong predictor of vascular morbidity and mortality. Toxic effects of hyperhomocysteinemia on the vascular wall can be explained by a chemical modification of lipoproteins and vascular structure, oxidative stress, endothelial dysfunction, inadequate endothelial cell regeneration, smooth muscle cell proliferation or by an accumulation of functionally non sufficient connective tissue. Also thrombogenic effects or an increased

expression of cholesterol level controlling proteins and fatty acids in the liver can be considered. Treatment of hyperhomocysteinemia is based on the administration of pharmacological doses of folic acid, B6 and B12 vitamins, which can decrease total homocysteine concentration by 25 to 30%. Such decrease, which is in average 3 micromol/l, results in the decrease of relative risk of ischaemic heart disease by 11 to 16%, phlebothrombosis by 25% and vascular brain diseases by 19 to 24%.

Cas Lek Cesk. 2004;143(6):367-74

FRESH ORGANICALLY GROWN GINGER (ZINGIBER OFFICINALE): COMPOSITION AND EFFECTS ON LPS-INDUCED PGE2 PRODUCTION.

Gas chromatography in conjunction with mass spectrometry, a technique previously employed to analyze non-volatile pungent components of ginger extracts modified to trimethylsilyl derivatives, was applied successfully for the first time to analyze unmodified partially purified fractions from the dichloromethane extracts of organically grown samples of fresh Chinese white and Japanese yellow varieties of ginger, *Zingiber officinale* Roscoe (Zingiberaceae). This analysis resulted in the detection of 20 hitherto unknown natural products and 31 compounds previously reported as ginger constituents. These include paradols, dihydroparadols, gingerols, acetyl derivatives of gingerols, shogaols, 3-dihydroshogaols, gingerdiols, mono- and diacetyl derivatives of gingerdiols, 1-dehydrogingerdiols, diarylheptanoids, and methyl ether derivatives of some of these compounds. The thermal degradation of gingerols to gingerone, shogaols, and related compounds was demonstrated. The major constituent in the two varieties was [6]-gingerol, a chemical marker for *Z. officinale*. Mass spectral fragmentation patterns for all the compounds are described and interpreted. Anti-inflammatory activities of silica gel chromatography fractions were tested using an *in vitro* PGE2 assay. Most of the fractions containing gingerols and/or gingerol derivatives showed excellent inhibition of LPS-induced PGE2 production.

Phytochemistry. 2004 Jul;65(13):1937-54

MAGNESIUM IN CARDIOVASCULAR AND OTHER DISORDERS.

PURPOSE: The physiological role and metabolism of magnesium, the causes of magnesium deficiency, clinical data on the benefits of magnesium supplementation, and the management of magnesium deficiency are discussed. **SUMMARY:** Magnesium is an often overlooked electrolyte that is essential to life. Magnesium plays a role in more than 300 enzymatic reactions and is critically involved in energy metabolism, glucose utilization, protein synthesis, fatty acid synthesis and breakdown, ATPase functions, and virtually all hormonal reactions. Magnesium is closely involved in maintaining cellular ionic balance through its association with sodium, potassium, and calcium. Deficiency of magnesium is becoming more common in the US population and may be attributed to decreased dietary consumption and the use of diuretics; in the elderly, magnesium deficiency may be a consequence of reduced appetite, decreased mitochondrial respiratory activity, and increased myocardial collagen. Conditions that may be associated with magnesium deficiency include hypertension, congestive heart failure, arrhythmia, myocardial infarction, diabetes mellitus, and preeclampsia; in many of these, magnesium supplementation has been found beneficial in clinical studies. Supplementation should be considered for patients with risk factors for deficiency and should be instituted for patients showing symptoms of deficiency. In addition to instituting supplementation when appropriate, the clinician should identify and correct the underlying cause of the deficiency. **CONCLUSION:** Magnesium deficiency may contribute to pathological processes. Clinicians should consider using magnesium supplementation to prevent deficiency in patients at risk and to treat deficiency when it occurs.

Am J Health Syst Pharm. 2004 Aug 1;61(15):1569-76

ORGANOSELENIUM COMPOUNDS AS POTENTIAL THERAPEUTIC AND CHEMOPREVENTIVE AGENTS: A REVIEW.

Selenium (Se) is an essential trace element. It is, however toxic at concentration little above which is required for health. Selenium is incorporated into proteins as selenocysteine, the 21(st) amino acid. Selenoproteins are found in bacteria, archaea, and eukaryotes. Biochemical and physicochemical properties of selenium result in the unique redox characteristics of selenocysteine and its use in antioxidant enzymes. In this context of a redox reaction is the reduction of reactive oxygen metabolites by glutathione peroxidases, helping to maintain membrane integrity, reduces the oxidative damage to lipids, lipoproteins, and DNA. Selenium has structural and enzymatic roles. Selenium influences a number of endocrine processes, most notably, those involved in thyroid hormone synthesis and metabolism. Se is needed for the proper functioning of the immune system, a role in viral suppression, AIDS, and also is implicated in delaying the aging process. Its deficiency has been linked to a number of disorders such as heart disease, diabetes, and diseases of the liver, and it is required for sperm motility and may reduce the risk of miscarriage. Se supplementation has recently moved from the realm of correcting nutritional deficiencies to one of pharmacological intervention, especially in the clinical domain of cancer chemoprevention. During the last few years, a tremendous effort has been directed toward the synthesis of stable organoselenium compounds that could be used as antioxidants, enzyme modulators, antitumor, antimicrobials, antihypertensive agents, antivirals and cytokine inducers. The

biochemistry and pharmacology of selenium-based compounds are subjects of intense current interest, especially from the point of view of public health. The purpose of this review is to discuss the recent pharmacological applications of organoselenium compounds as therapeutic agents in the treatment of several diseases.

Curr Med Chem. 2004 Jun;11(12):1657-69

SELENIUM BIOCHEMISTRY AND CANCER: A REVIEW OF THE LITERATURE.

In recent years, the role of selenium in the prevention of a number of degenerative conditions including cancer, inflammatory diseases, thyroid function, cardiovascular disease, neurological diseases, aging, infertility, and infections, has been established by laboratory experiments, clinical trials, and epidemiological data. Most of the effects in these conditions are related to the function of selenium in antioxidant enzyme systems. Replenishing selenium in deficiency conditions appears to have immune-stimulating effects, particularly in patients undergoing chemotherapy. However, increasing the levels of selenoprotein antioxidant enzymes (glutathione peroxidase, thioredoxin reductase, etc.) appears to be only one of many ways in which selenium-based metabolites contribute to normal cellular growth and function. Animal data, epidemiological data, and intervention trials have shown a clear role for selenium compounds in both prevention of specific cancers and antitumorigenic effects in post-initiation phases of cancer.

Altern Med Rev. 2004 Sep;9(3):239-58

ABSTRACTS

Green tea extract

INHIBITION OF LUNG CARCINOGENESIS AND EFFECTS ON ANGIOGENESIS AND APOPTOSIS IN A/J MICE BY ORAL ADMINISTRATION OF GREEN TEA.

Oral administration of tea (*Camellia sinensis*) has been shown to inhibit the formation and growth of several tumor types in animal models. The present study investigated the effects of treatment with different concentrations of green tea on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis in female A/J mice. Two days after a single dose of NNK (100 mg/kg body weight, i.p.), the mice were given 0.1, 0.2, 0.4, and 0.6% green tea solution (1, 2, 4, and 6 g of tea solids, respectively, dissolved in 1 l of water), 0.02% caffeine, or water as the sole source of drinking fluid until the termination of the experiment. Only the treatment with 0.6% tea preparation significantly reduced lung tumor multiplicity (mean \pm SE, 6.07 \pm 0.77 vs. 8.60 \pm 0.50 tumors per mouse, $P = 0.018$). Treatment with 0.6% tea also inhibited angiogenesis, as indicated by the lower microvessel density (number of blood vessels/mm²) based on immunostaining for the von Willebrand factor antigen (81.9 \pm 9.5 vs. 129.4 \pm 8.2, $P = 0.0018$) and anti-CD31 antibody staining (465.3 \pm 61.4 vs. 657.1 \pm 43.6, $P = 0.0012$). Significantly lower vascular endothelial growth factor immunostaining scores were also observed in the 0.6% tea-treated group (0.98 \pm 0.17 vs. 1.43 \pm 0.07, $P = 0.006$). The apoptosis index was significantly higher in lung adenomas from 0.6% tea-treated mice based on morphological analysis of cell apoptosis (2.51 \pm 0.18% vs. 1.57 \pm 0.11%, $P = 0.00005$), and the result was further confirmed using the TUNEL method. Inhibition of angiogenesis and the induction of apoptosis by green tea may be closely related to the inhibition of pulmonary carcinogenesis.

Nutr Cancer. 2004;48(1):44-53

UPDATE ON CHEMOPREVENTION OF PROSTATE CANCER.

PURPOSE OF REVIEW: Prostate cancer remains the most commonly diagnosed visceral cancer in men in the United States, with almost 200,000 newly diagnosed cases in 2003. Prevention of this disease would have a major impact on disease-associated cost, morbidity, and mortality for a large segment of the population. A major advance in prevention of prostate cancer came in 2003 with the publication of the Prostate Cancer Prevention Trial. This overview summarizes the results of that trial, the design of other large-scale trials, and advances in understanding of the molecular mechanisms underlying the effect of other promising agents. **RECENT FINDINGS:** The Prostate Cancer Prevention Trial demonstrated that use of finasteride is associated with a 25% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years with normal digital rectal exam and initial prostate specific antigen <3.0 ng/ml. Use of finasteride was associated with a slightly higher risk of Gleason sum 7-10 tumors, some sexual side effects, and fewer urinary symptoms. A substantial body of new molecular evidence supports the existing body of clinical and epidemiological data leading to testing of vitamin E and selenium as preventative agents in men at risk for prostate cancer. Epidemiologic and molecular evidence also makes cyclooxygenase-2 inhibitors, lycopene, soy, and green tea promising agents. **SUMMARY:** Results of a population-based, randomized phase III trial demonstrates that finasteride can prevent prostate cancer. A large amount of data supports the use of other agents as potential preventatives, including selenium, vitamin E, vitamin D, other 5- α -reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene, and green tea. Some of these agents are being tested in new large-scale phase III clinical trials.

Curr Opin Urol. 2004 May;14(3):143-9

EGCG DOWN-REGULATES TELOMERASE IN HUMAN BREAST CARCINOMA MCF-7 CELLS, LEADING TO SUPPRESSION OF CELL VIABILITY AND INDUCTION OF APOPTOSIS.

Telomerase is elevated in >90% of breast carcinomas and therefore has received much attention as a target for breast cancer therapy and cancer diagnostic research. Dietary components that are capable of inhibiting the growth of cancer cells without affecting the growth of normal cells are receiving considerable attention in developing novel cancer-preventive approaches. Studies have shown that (-)-epigallocatechin-3-gallate (EGCG) from green tea imparts a growth inhibitory effect on cancer cells. Here, we show that treatment of EGCG dose-dependently inhibited (20-100%) the reproductive or colony forming potential, and also decreased cell viability at different time points studied (approximately 80% inhibition) in human breast carcinoma MCF-7 cells but had no adverse effect on the growth of normal mammary cells. Treatment of EGCG for 48 and 72 h markedly increased the percentage of apoptotic cells (32-51%) in MCF-7 cells compared to that of non-EGCG treated cells (8-14%). In order to identify the possible mechanism of decreased cell viability and induction of apoptosis in breast carcinoma cells by EGCG, we found that treatment of MCF-7 cells with EGCG dose-dependently inhibited telomerase activity (40-55%), and also inhibited the mRNA expression (40-55%) of hTERT, a catalytic subunit of telomerase. Additional studies demonstrated that EGCG also inhibited the protein expression of hTERT, which indicated that inhibition of telomerase was associated with down-regulation of hTERT.

Together, our results indicate that EGCG down-regulates telomerase in human breast carcinoma MCF-7 cells, leading to the suppression of cell viability and induction of apoptosis, thus providing the molecular basis for the development of EGCG as a novel chemopreventive and pharmacologically safe agent against breast cancer.

Int J Oncol. 2004 Mar;24(3):703-10

HTLV-1 PROVIRUS LOAD IN PERIPHERAL BLOOD LYMPHOCYTES OF HTLV-1 CARRIERS IS DIMINISHED BY GREEN TEA DRINKING.

Human T-cell lymphotropic virus type 1 (HTLV-1) is causatively associated with adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Since a high level of HTLV-1 provirus load in circulating lymphocytes is thought to be a risk for ATL and HAM/TSP, diminution of HTLV-1 provirus load in the circulation may prevent these intractable diseases. Our previous study (Jpn J Cancer Res 2000; 91: 34-40) demonstrated that green tea polyphenols inhibit in vitro growth of ATL cells, as well as HTLV-1-infected T-cells. The present study aimed to investigate the in vivo effect of green tea polyphenols on HTLV-1 provirus load in peripheral blood lymphocytes on HTLV-1 carriers. We recruited 83 asymptomatic HTLV-1 carriers to examine HTLV-1 provirus DNA with or without administration of capsulated green tea extract powder. Thirty-seven subjects were followed up for 5 months by measuring HTLV-1 provirus load after daily intake of 9 capsules of green tea extract powder per day (equivalent to 10 cups of regular green tea), and 46 subjects lived ad libitum without intake of any green tea capsule. The real-time PCR quantification of HTLV-1 DNA revealed a wide range of variation of HTLV-1 provirus load among asymptomatic HTLV-1 carriers (0.2-200.2 copies of HTLV-1 provirus load per 1000 peripheral blood lymphocytes). Daily intake of the capsulated green tea for 5 months significantly diminished the HTLV-1 provirus load as compared with the controls ($P = 0.031$). These results suggest that green tea drinking suppresses proliferation of HTLV-1-infected lymphocytes in vivo.

Cancer Sci. 2004 Jul;95(7):596-601

GREEN AND BLACK TEAS INHIBIT ATHEROSCLEROSIS BY LIPID, ANTIOXIDANT, AND FIBRINOLYTIC MECHANISMS.

Tea is the most widely consumed beverage in the world, second only to water. Most laypersons and scientists believe that green tea is healthier than black tea due to the low incidence of heart disease and cancer in the Orient. Here, we report the first dose-response comparison of a green and black tea on normal hamsters after long-term supplementation and on a hamster model of atherosclerosis. Both teas were equally effective in inhibiting atherosclerosis with the lower dose decreasing it 26-46% and the high dose decreasing it 48-63%. Athero-sclerosis was inhibited by three mechanisms: hypolipemic, antioxidant, and antifibrinolytic. There was a significant correlation between atherosclerosis and the three mechanisms. In the normal animals, teas also caused some improvement in plasma low density lipoprotein (LDL), LDL/high density lipoprotein ratio, triglycerides, lipid peroxides, lower density lipoprotein lipid peroxides, and fibrinogen. Isolated lower density lipoprotein oxidizability was also reduced in all groups. Green and black teas were equally effective at human equivalent doses, thus confirming human intervention and epidemiology studies and providing mechanisms for teas' benefit.

J Agric Food Chem. 2004 Jun 2;52(11):3661-5

EFFECTS OF GREEN TEA INTAKE ON THE DEVELOPMENT OF CORONARY ARTERY DISEASE.

BACKGROUND: Green tea, a popular beverage in Japan, contains many polyphenolic antioxidants, which might prevent atherosclerosis. This study was designed to determine whether the consumption of green tea is proportionately associated with a decreased incidence of coronary artery disease (CAD) and the cardiovascular and cerebrovascular prognosis. **METHODS AND RESULTS:** The study group comprised 203 patients who underwent coronary angiography (109 patients with significant coronary stenosis and 94 patients without). Predictors for CAD were analyzed and the patients' cardiovascular and cerebrovascular events were followed. Green tea consumption was significantly higher in patients without CAD than in those with CAD (5.9 ± 0.5 vs 3.5 ± 0.3 cups/day; $p < 0.001$). An inverse relationship between the intake of green tea and the incidence of CAD was observed ($p < 0.001$). The green tea intake per day was an independent predictor for CAD based on a multivariate logistic regression analysis (odds ratio: 0.84 and 95% confidence interval: 0.76-0.91). In contrast, the green tea intake was not a predictor of cardiovascular and cerebrovascular events based on the Cox proportional hazard model. **CONCLUSIONS:** Green tea consumption was associated with a lower incidence of CAD in the present study population in Japan. Therefore, the more green tea patients consume, the less likely they are to have CAD.

Circ J. 2004 Jul;68(7):665-70

DIFFERENTIAL EFFECTS OF GREEN TEA-DERIVED CATECHIN ON DEVELOPING VERSUS ESTABLISHED ATHEROSCLEROSIS IN APOLIPOPROTEIN E-NULL MICE.

BACKGROUND: Oxidative stress has been implicated in vascular injury and atherogenesis, and antioxidant treatment has shown

favorable results in preclinical studies. Despite this, antioxidant therapy has failed to show benefit in clinical trials. Failure of antioxidants in clinical trials may be partly because such therapy is started after atherosclerosis is already well established, whereas the benefits in animal models may be results from early initiation of antioxidants while atherosclerosis is still evolving.

METHODS AND RESULTS: To test this hypothesis, we evaluated the effect of epigallocatechin gallate (EGCG), the main antioxidant derived from green tea, on evolving and established atherosclerotic lesions in hypercholesterolemic apolipoprotein E-null mice. Established native aortic atherosclerotic lesions and evolving atherosclerotic lesions produced by periaortic cuff injury to carotid arteries were assessed in mice after 21 and 42 days of treatment with daily intraperitoneal injections of EGCG (10 mg/kg) or PBS. EGCG treatment resulted in an increase in the antioxidant capacity in local vascular tissue and systemic circulation and reduced vascular smooth muscle cell proliferation and redox-sensitive gene activation in vitro. EGCG reduced cuff-induced evolving atherosclerotic plaque size at 21 and 42 days by 55% and 73%, respectively, compared with PBS treatment ($P < 0.05$). Conversely, EGCG had no effect on established lesions in the aortic sinuses or the rest of the aorta.

CONCLUSIONS: Our data suggest that antioxidant EGCG differentially reduces evolving atherosclerotic lesions without influencing established atherosclerosis in the apolipoprotein E-null mice.

Circulation. 2004 May 25;109(20):2448-53

ABSTRACTS

Heart disease and depression

EVOLVING CONCEPTS IN THE TRIAD OF ATHEROSCLEROSIS, INFLAMMATION AND THROMBOSIS.

Recent developments into athero-thrombosis, the leading cause of morbidity and mortality in Western Society, may help to change our treatment strategy to a more casual approach. The composition of the atherosclerotic plaque, rather than the percent stenosis, appears to be a critical predictor for both risk of plaque rupture and subsequent thrombogenicity. A large lipid core, rich in tissue factor (TF) and inflammatory cells including macrophages, and a thin fibrous cap with compromise of its structural integrity by matrix degrading enzymes, such as metalloproteinases (MMPs), render a lesion susceptible to rupture and subsequent acute thrombosis. Thrombosis may lead to a complete occlusion or, in the case of mural thrombus or intraplaque hemorrhage, to plaque progression. Disruption of a vulnerable or unstable plaque (type IV and Va lesions of the AHA classification) with a subsequent change in plaque geometry and thrombosis may result in an acute coronary syndrome. The high-risk plaque tend to be relatively small, but soft or vulnerable to "passive" disruption because of high lipid content. Inflammatory processes are important components of all stages of atherosclerotic development, including plaque initiation and disruption. As such the early steps in atherosclerotic lesion formation are the over expression of endothelial adhesive protein (i.e. selectins, VCAM and ICAM), chemotactic factors (MCP-1), growth factors (M-CSF), and cytokines (IL-2) that will facilitate the recruitment, internalization and survival of blood-borne inflammatory cells into the vascular wall. Macrophages, following what appears to be a defense mission by protecting the vessel wall from excess lipid accumulation, may eventually undergo apoptosis with release of MMPs and TF. Specific cell recruitment in the vessel wall and build-up of the extracellular matrix are coordinated by a wide variety of stimulators and inhibitors. Active interaction of immune competent cells within the atherosclerotic lesions appears to play a pivotal role in the control of atherosclerotic plaque evolution and, therefore, deserves particular attention from the research community with the ultimate goal of improving preventive and therapeutic medical approaches. Inflammation, thrombosis and atherosclerosis are interdependent and define a triad within the complex pathogenic process of athero-thrombosis.

J Thromb Thrombolysis. 2004 Feb;17(1):35-44

HIGH-SENSITIVITY C-REACTIVE PROTEIN, INFLAMMATION, AND CARDIOVASCULAR RISK: FROM CONCEPT TO CLINICAL PRACTICE TO CLINICAL BENEFIT.

Advances in vascular biology have shown that inflammation plays an integral role in the development of cardiovascular disease. Extensive study of high-sensitivity C-reactive protein (hs-CRP) has demonstrated that this measure of inflammation predicts cardiovascular risk not reflected by traditional risk factors, adds prognostic information to traditional risk assessment, and predicts long-term cardiovascular risk in individuals with no prior evidence of cardiovascular disease. Patients with elevated hs-CRP levels in the absence of elevated cholesterol appear to derive preventive benefit from statin therapy that is similar in magnitude to that in patients with elevated cholesterol. The large-scale Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosvastatin (JUPITER) trial represents a critical study to determine the utility of a strategy for targeting statin therapy to prevent incident cardiovascular disease in patients at increased cardiovascular risk on the basis of elevated hs-CRP who would not be considered candidates for therapy on the basis of hypercholesterolemia or traditional risk assessment. Inclusion of hs-CRP measurement in risk screening and use of this information to guide preventive therapy could result in a marked improvement in prevention of cardiovascular morbidity and mortality.

Am Heart J. 2004 Jul;148(1 Suppl):S19-26

BLOCKING CARBOHYDRATE ABSORPTION AND WEIGHT LOSS: A CLINICAL TRIAL USING PHASE 2 BRAND PROPRIETARY FRACTIONATED WHITE BEAN EXTRACT.

Background: Phase 2' starch neutralizer brand bean extract product ("Phase 2") is a water-extract of a common white bean (*Phaseolus vulgaris*) that has been shown in vitro to inhibit the digestive enzyme alpha-amylase. Inhibiting this enzyme may prevent the digestion of complex carbohydrates, thus decreasing the number of carbohydrate calories absorbed and potentially promoting weight loss. Methods: Fifty obese adults were screened to participate in a randomized, double-blind, placebo-controlled study evaluating the effects of treatment with Phase 2 versus placebo on weight loss. Participants were randomized to receive either 1500 mg Phase 2 or an identical placebo twice daily with meals. The active study period was eight weeks. Thirty-nine subjects completed the initial screening process and 27 subjects completed the study. Results: The results after eight weeks demonstrated the Phase 2 group lost an average of 3.79 lbs (average of 0.47 lb per week) compared with the placebo group, which lost an average of 1.65 lbs (average of 0.21 lb per week), representing a difference of 129% ($p=0.35$). Triglyceride levels in the Phase 2 group were reduced an average of 26.3 mg/dL, more than three times greater a reduction than observed in the placebo group (8.2 mg/dL) ($p=0.07$). No adverse events during the study were attributed to the study medication. Conclusion:

Clinical trends were identified for weight loss and a decrease in triglycerides, although statistical significance was not reached. Phase 2 shows potential promise as an adjunct therapy in the treatment of obesity and hypertriglyceridemia and further studies with larger numbers of subjects are warranted to conclusively demonstrate effectiveness.

Altern Med Rev. 2004 Mar;9(1):63-9

DEPRESSION IN AGING MEN: THE ROLE OF TESTOSTERONE.

Age-related decline in testosterone levels is associated with a number of mild, nonspecific symptoms, including depressive symptoms. The relationship between depressive symptoms and testosterone levels is confounded by numerous factors, including medical illness, obesity, smoking, alcohol use, diet, and stress, and is thus complex. Studies have not consistently supported an integral role of reduced testosterone levels in major depressive disorder, although levels may often be reduced in men with treatment-refractory depression and older men with dysthymia. Low testosterone levels may also increase the risk of incident depression in older males, although this may depend upon androgen receptor genetic polymorphisms. Testosterone replacement has demonstrated short-term tolerability and efficacy in augmenting antidepressants to alleviate treatment-refractory depression in adult males. Case studies support the potential need for maintenance therapy to maintain response. In a placebo-controlled trial, testosterone monotherapy was not effective in treating major depressive disorder in men with hypogonadism. However, in an open-label, noncomparative study, testosterone monotherapy appeared effective in treating late-onset but not early-onset major depressive disorder in older males. Testosterone therapy is not without potential for adverse effects, the most worrisome of which is the worsening of pre-existing prostate carcinoma. Oral, short- and long-acting parenteral, and transdermal patch and gel formulations are available. Testosterone has demonstrated usefulness in the treatment of a number of depressed populations, but further studies are needed to fully elucidate its role in the treatment of depressive syndromes in the aging male.

Drugs Aging. 2004;21(6):361-76

CHANGES IN SEX HORMONE-BINDING GLOBULIN AND TESTOSTERONE DURING WEIGHT LOSS AND WEIGHT MAINTENANCE IN ABDOMINALLY OBESE MEN WITH THE METABOLIC SYNDROME.

BACKGROUND: Mild hypoandrogenism in men, usually defined by low levels of testosterone, is a peculiar feature of abdominal obesity that independently predicts the development of insulin resistance and diabetes mellitus. Little is known about the short- and long-term effects of weight loss on sex steroids in abdominally obese men, however. **OBJECTIVES:** We assessed the effect of rapid weight loss and sustained weight maintenance on the plasma concentrations of testosterone and other sex hormones in 58 abdominally obese men (age, 46.3 +/- 7.5 years; body mass index, 36.1 +/- 3.8 kg/m²; waist girth, 121 +/- 10 cm) with the metabolic syndrome. **RESULTS:** The men lost on average 16.3 +/- 4.5 kg during a 9-week very low-calorie diet (VLCD) and maintained 14.3 +/- 9.1 kg weight loss after a 12-month maintenance period (vs. baseline, $p < 0.001$). Sex hormone-binding globulin (SHBG) increased from 27.6 +/- 11.9 to 48.1 +/- 23.5 nmol/l during the VLCD but decreased to 32.6 +/- 12.9 nmol/l during weight maintenance, which was still higher than at baseline ($p < 0.001$). Free testosterone (fT) increased from 185 +/- 66 to 208 +/- 70 pmol/l ($p = 0.002$) during the VLCD and remained high after 1 year of weight maintenance (212 +/- 84 pmol/l, $p = 0.002$). Total testosterone levels followed a pattern intermediate between fT and SHBG. Plasma estradiol and dehydroepiandrosterone sulphate concentrations changed only transiently or not at all. **CONCLUSIONS:** Rapid weight loss with successful weight maintenance in abdominally obese men with the metabolic syndrome brings about a sustained increase in fT levels. The dramatic increase in SHBG attenuated initially during weight maintenance but remained elevated. These findings may be important with regard to prevention of progressive metabolic decompensation and cardiovascular disease associated with obesity and the metabolic syndrome.

Diabetes Obes Metab. 2004 May;6(3):208-15

CARNITINE VERSUS ANDROGEN ADMINISTRATION IN THE TREATMENT OF SEXUAL DYSFUNCTION, DEPRESSED MOOD, AND FATIGUE ASSOCIATED WITH MALE AGING.

OBJECTIVES: To compare testosterone undecanoate versus propionyl-L-carnitine plus acetyl-L-carnitine and placebo in the treatment of male aging symptoms. **METHODS:** A total of 120 patients were randomized into three groups. The mean patient age was 66 years (range 60 to 74). Group 1 was given testosterone undecanoate 160 mg/day, the second group was given propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group was given a placebo (starch). Drugs and placebo were given for 6 months. The assessed variables were total prostate-specific antigen, prostate volume, peak systolic velocity, end-diastolic velocity, resistive index of cavernosal penile arteries, nocturnal penile tumescence, total and free testosterone, prolactin, luteinizing hormone, International Index of Erectile Function score, Depression Melancholia Scale score, fatigue scale score, and incidence of side effects. The assessment was performed at intervals before, during, and after therapy. **RESULTS:** Testosterone and carnitines significantly improved the peak systolic velocity, end-diastolic velocity, resistive index, nocturnal penile tumescence, International Index of Erectile Function score, Depression Melancholia Scale score, and fatigue scale score. Carnitines proved significantly more active than testosterone in improving nocturnal penile tumescence and International Index of Erectile Function score. Testosterone significantly increased the prostate volume and free and total testosterone levels and

significantly lowered serum luteinizing hormone; carnitines did not. No drug significantly modified prostate-specific antigen or prolactin. Carnitines and testosterone proved effective for as long as they were administered, with suspension provoking a reversal to baseline values. Only the group 1 prostate volume proved significantly greater than baseline 6 months after testosterone suspension. Placebo administration proved ineffective. Negligible side effects emerged. **CONCLUSIONS:** Testosterone and, especially, carnitines proved to be active drugs for the therapy of symptoms associated with male aging.

Urology. 2004 Apr;63(4):641-6

DEPRESSION AS A RISK FACTOR FOR CORONARY ARTERY DISEASE: EVIDENCE, MECHANISMS, AND TREATMENT.

OBJECTIVE: The present paper reviews the evidence that depression is a risk factor for the development and progression of coronary artery disease (CAD). **METHODS:** MEDLINE searches and reviews of bibliographies were used to identify relevant articles. Articles were clustered by theme: depression as a risk factor, biobehavioral mechanisms, and treatment outcome studies. **RESULTS:** Depression confers a relative risk between 1.5 and 2.0 for the onset of CAD in healthy individuals, whereas depression in patients with existing CAD confers a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality. A number of plausible biobehavioral mechanisms linking depression and CAD have been identified, including treatment adherence, lifestyle factors, traditional risk factors, alterations in autonomic nervous system (ANS) and hypothalamic pituitary adrenal (HPA) axis functioning, platelet activation, and inflammation. **CONCLUSION:** There is substantial evidence for a relationship between depression and adverse clinical outcomes. However, despite the availability of effective therapies for depression, there is a paucity of data to support the efficacy of these interventions to improve clinical outcomes for depressed CAD patients. Randomized clinical trials are needed to further evaluate the value of treating depression in CAD patients to improve survival and reduce morbidity.

Psychosom Med. 2004 May-Jun;66(3):305-15

ABSTRACTS**SAMe****SEVERE ADVERSE DRUG REACTIONS OF ANTIDEPRESSANTS: RESULTS OF THE GERMAN MULTICENTER DRUG SURVEILLANCE PROGRAM AMSP.**

The goal of the German drug safety program in psychiatry AMSP (Arzneimittelsicherheit in der Psychiatrie) is the assessment of severe or new adverse drug reactions (ADRs). Here we report on 53,042 of 122,562 patients treated with antidepressants who were monitored from 1993 to 2000 in 35 psychiatric hospitals in German-speaking countries. The overall incidence of severe ADRs of antidepressants was 1.4% of exposed patients; when only ADRs rated as probable or definite were considered, a rate of 0.9% in patients treated with antidepressants was observed. ADR rates were higher for TCAs (imputed in 1.0% of patients overall, respectively in 0.6 % of patients when only ADs were imputed) and lower for MAO inhibitors and SSRIs (0.7% for both, respectively 0.3% and 0.4%). Within the TCA group there was a difference among clomipramine (2.1%, respectively 1.0%), amitriptyline (1.0%, respectively 0.6%), and doxepin or trimipramine (both 0.6%, respectively 0.3%). With regard to single SSRI, similar rates were observed for paroxetine (0.8%, respectively 0.5%) and for citalopram (0.7%, respectively 0.4%). Of the new dual-acting antidepressants, venlafaxine ranged at 0.9%, (respectively 0.5%) and mirtazapine at 0.6 % (respectively 0.5%). In particular, TCAs were associated with known risks, such as toxic delirium, grand mal seizures, and hepatic (i.e., increased liver enzymes), urologic (i.e., urinary retention), allergic (i.e., exanthema), or cardiovascular (i.e., mainly orthostatic collapse) reactions. In SSRI-treated patients (non-delirious) psychic and neurological ADRs were most prominent, followed by gastrointestinal, dermatologic, and endocrinological/electrolyte reactions, with agitation, hyponatremia (probably as part of the SIADH syndrome and associated with severe neurologic or psychiatric symptoms in 64% of all cases), increased liver enzymes, nausea, and the serotonin syndrome as leading unwanted symptoms. Venlafaxine (in the immediate-release formulation) was associated with adverse CNS and somatic symptoms such as severe agitation, diarrhea, increased liver enzymes, hypertension, and hyponatremia. Mirtazapine was mostly connected with increased liver enzymes, cutaneous edema, and collapse, but with no case of significant hyponatremia. For drugs that potently inhibit serotonin uptake, serum sodium concentration should be controlled when applied in high-dose therapy or in vulnerable patients.

Pharmacopsychiatry. 2004 Mar;37 Suppl 1:S39-45

SERUM FOLATE, VITAMIN B12, AND HOMOCYSTEINE IN MAJOR DEPRESSIVE DISORDER, PART 2: PREDICTORS OF RELAPSE DURING THE CONTINUATION PHASE OF PHARMACOTHERAPY.

OBJECTIVE: In the present study, we assessed the relationship between serum folate, vitamin B12, and homocysteine levels on the rate of relapse in outpatients with remitted major depressive disorder (MDD) during a 28-week continuation phase of treatment with fluoxetine. **METHOD:** Seventy-one outpatients (mean +/- SD age = 40.2 +/- 11.1 years; 56.3% women) with MDD (as assessed with the Structured Clinical Interview for DSM-III-R) who had remitted and who were enrolled in the continuation phase of treatment with fluoxetine had serum folate, vitamin B12, and homocysteine measurements completed at baseline (prior to acute-phase treatment). Patients were followed for 28 weeks of continued treatment with fluoxetine 40 mg/day to monitor for depressive relapse. Folate levels were classified as either low (< or = 2.5 ng/mL) or normal. Vitamin B12 levels were classified as either low (< or = 200 pg/mL) or normal. Homocysteine levels were classified as either elevated (> or = 13.2 micromol/L) or normal. With the use of separate logistic regressions, we then assessed the relationship between folate, vitamin B12, and homocysteine level status and relapse. The study was conducted from November 1992 to January 1999. **RESULTS:** The presence of low serum folate levels ($p = .004$), but not low B12 ($p > .05$) or elevated homocysteine levels ($p > .05$), was associated with relapse during continuation treatment with fluoxetine. The relapse rates for patients with ($N = 7$) and without ($N = 64$) low folate levels were 42.9% versus 3.2%, respectively. **CONCLUSION:** Low serum folate levels were found to place patients with remitted MDD at risk for depressive relapse during the continuation phase of treatment with fluoxetine.

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ADVANCES IN ALCOHOLIC LIVER DISEASE.

Cytokines are mediators of cellular communication produced by multiple liver cell types. Cytokines can directly induce either necrosis or apoptosis. They can also recruit such cells as neutrophils and lymphocytes, which can mediate liver damage. Increased levels of hepatotoxic cytokines such as tumor necrosis factor-alpha are documented in alcoholic liver disease (ALD) and nonalcoholic steatohepatitis (NASH) and have been shown to play a mechanistic role in both of these disease processes. Transforming growth factor-beta is a profibrotic cytokine that is critical in hepatic fibrosis. Beneficial cytokines, such as interleukin (IL)-10 and -6, also exist. Such beneficial cytokines as adiponectin are made outside the liver and appear to protect against ALD and NASH. This article reviews the relevance of cytokines in human and experimental forms of liver injury, focusing

on modulation of cytokines and the use of beneficial cytokines in treatment and prevention of liver injury in ALD, NASH, and hepatitis C.

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INHIBITION OF LIPOPOLYSACCHARIDE-STIMULATED TNF-ALPHA PROMOTER ACTIVITY BY S-ADENOSYLMETHIONINE AND 5'-METHYLTHIOADENOSINE.

S-adenosylmethionine (SAME) is the principal biological methyl donor and precursor for polyamines. SAME is known to be hepatoprotective in many liver disease models in which TNF-alpha is implicated. The present study investigated whether and how SAME inhibited LPS-stimulated TNF-alpha expression in Kupffer cells (hepatic macrophages). SAME downregulated TNF-alpha expression in LPS-stimulated Kupffer cells at the transcriptional level as suggested by a transfection experiment with a TNF-alpha promoter-reporter gene. This inhibition was not mediated through decreased NF-kappaB binding to four putative kappaB binding elements located within the promoter. The inhibited promoter activity was neither prevented by overexpression of p65 and/or its coactivator p300 nor enhanced by overexpression of coactivator-associated arginine methyltransferase-1, an enzyme that methylates p300 and inhibits a p65-p300 interaction. SAME did not lead to DNA methylation at the most common CpG target sites in the TNF-alpha promoter. Moreover, 5'-methylthioadenosine (MTA), which is derived from SAME but does not serve as a methyl donor, recapitulated SAME's effect with more potency. These data demonstrate that SAME inhibits TNF-alpha expression at the level downstream of NF-kappaB binding and at the level of the promoter activity via mechanisms that do not appear to involve the limited availability of p65 or p300. Furthermore, our study is the first to demonstrate a potent inhibitory effect on NF-kappaB promoter activity and TNF-alpha expression by a SAME's metabolite, MTA.

Am J Physiol Gastrointest Liver Physiol. 2004 Aug;287(2):G352-62.

5'-METHYLTHIOADENOSINE MODULATES THE INFLAMMATORY RESPONSE TO ENDOTOXIN IN MICE AND IN RAT HEPATOCYTES.

5'-methylthioadenosine (MTA) is a nucleoside generated from S-adenosylmethionine (AdoMet) during polyamine synthesis. Recent evidence indicates that AdoMet modulates in vivo the production of inflammatory mediators. We have evaluated the anti-inflammatory properties of MTA in bacterial lipopolysaccharide (LPS) challenged mice, murine macrophage RAW 264.7 cells, and isolated rat hepatocytes treated with pro-inflammatory cytokines. MTA administration completely prevented LPS-induced lethality. The life-sparing effect of MTA was accompanied by the suppression of circulating tumor necrosis factor-alpha (TNF-alpha), inducible NO synthase (iNOS) expression, and by the stimulation of IL-10 synthesis. These responses to MTA were also observed in LPS-treated RAW 264.7 cells. MTA prevented the transcriptional activation of iNOS by pro-inflammatory cytokines in isolated hepatocytes, and the induction of cyclooxygenase 2 (COX2) in RAW 264.7 cells. MTA inhibited the activation of p38 mitogen-activated protein kinase (MAPK), c-jun phosphorylation, inhibitor kappa B alpha (IkappaBalpha) degradation, and nuclear factor kappaB (NFkappaB) activation, all of which are signaling pathways related to the generation of inflammatory mediators. These effects were independent of the metabolic conversion of MTA into AdoMet and the potential interaction of MTA with the cAMP signaling pathway, central to the anti-inflammatory actions of its structural analog adenosine. In conclusion, these observations demonstrate novel immunomodulatory properties for MTA that may be of value in the management of inflammatory diseases.

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GASTROINTESTINAL SIDE EFFECTS OF TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND NEW FORMULATIONS.

Although adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) occur in only a small proportion of users, the widespread use of these drugs has resulted in a substantial overall number of affected persons who experience serious gastrointestinal complications. Dyspeptic symptoms are estimated to occur in 10-60% of NSAID users and lead to discontinuation of treatment in 5-15% of rheumatoid arthritis patients taking NSAIDs. It is now well established that the point prevalence of peptic ulcer disease in patients receiving conventional NSAID therapy ranges between 10 and 30%, representing a 10-30-fold increase over that found in the general population. One of 175 users of conventional NSAIDs in the USA will be hospitalized each year for NSAID-induced gastrointestinal damage. The mortality of hospitalized patients remains about 5-10%, with an expected annual death rate of 0.08%. The selective COX-II inhibitors (rofecoxib, celecoxib, parecoxib, etoricoxib, valdecoxib, lumiracoxib) show consistently comparable efficacy to that of conventional non-steroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis and osteo-arthritis, but have a significantly reduced propensity to cause gastrointestinal toxicity. In many cases, the gastric effects of therapeutically active doses of COX-II inhibitors are indistinguishable from placebo. The safety benefits of COX-2 inhibitors given alone appear similar to combined therapy with conventional NSAIDs and gastroprotective agents. These findings warrant the consideration of COX-II inhibitors as first-line therapy in patients requiring long-term pain control.

THE LONG-TERM EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN OSTEOARTHRITIS OF THE KNEE: A RANDOMIZED PLACEBO-CONTROLLED TRIAL.

BACKGROUND: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat osteoarthritis (OA), though their long-term efficacy is uncertain. We report a comparison of the symptomatic responses to therapy with tiaprofenic acid, indomethacin and placebo over 5 yr. **METHODS:** A parallel-group, randomized, single-blind trial of patients with knee OA recruited 812 patients from 20 centres; 307 patients received tiaprofenic acid (300 mg b.d.), 202 indomethacin (25 mg t.d.s.) and 303 matching placebo for up to 5 yr. At the end of the parallel-group study, patients receiving tiaprofenic acid or placebo entered a 4-week blinded cross-over study of tiaprofenic acid or placebo, both given for 2 weeks. Assessments were at baseline, 4 weeks, then at 6-month intervals for up to 5 yr in the parallel group study and at 2-week intervals in the cross-over study. They comprised pain scores, duration of morning stiffness, patients' global assessments, paracetamol consumption, adverse reactions, withdrawals and functional outcomes. **RESULTS:** There were significant falls in overall pain scores in patients receiving NSAIDs compared with placebo at 4 weeks in the parallel-group phase. Thereafter there were no advantages favouring active therapy. In the cross-over phase, pain scores were significantly lower in patients receiving tiaprofenic acid than placebo. Patients who had been receiving long-term tiaprofenic acid showed significant rises in their pain scores when receiving placebo therapy and vice versa. Adverse events were reported by 61% of patients receiving tiaprofenic acid, 63% on indomethacin and 51% on placebo. Potentially severe side-effects were rare; for example, there were only three cases of gastrointestinal bleeding on NSAIDs. The pattern of withdrawal was similar in patients taking NSAIDs and placebo in the parallel-group study; at 48 weeks 53% of the patients remained on tiaprofenic acid, 50% on indomethacin and 54% on placebo. **CONCLUSIONS:** NSAIDs significantly reduce overall pain over 4 weeks. This short-term responsiveness is retained, and even after several years of therapy with tiaprofenic acid pain scores increased over 2 weeks when it was changed to placebo. Our results do not show long-term benefits from the use of NSAIDs in OA and the majority of patients had persisting pain and disability despite therapy.

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