

Abstracts

Recently Published Abstracts

Phospholipid association reduces the gastric mucosal toxicity of aspirin in human subjects.

Anand B, Romero JJ, Sanduja SK, Lichtenberger LM. *Am J Gastroenterol* 1999;94:1818-1822.

OBJECTIVE: In previous studies on rats, we have shown that aspirin (ASA)-induced injury to the gastric mucosa is markedly reduced or completely abolished if ASA is chemically associated with the phospholipid, phosphatidylcholine (PC). We have also shown that the protective effect of PC does not influence the ability of ASA to inhibit mucosal cyclooxygenase (COX) activity in the stomach and other tissues. We therefore sought to assess the effect of PC-associated ASA (ASA/PC) on the gastric mucosa of normal volunteers and to compare the results with the use of ASA alone. **METHODS:** Sixteen normal healthy subjects were administered ASA or ASA/PC in a randomized, double-blind, crossover study. The subjects received ASA in a dose of 650 mg three times a day for 3 days or an equivalent dose of ASA chemically associated with PC. Endoscopy was performed at baseline and again on the morning of day 4, after the subjects had taken the final dose of the test drug. On both occasions, antral biopsy specimens were obtained for the assessment of mucosal COX activity and prostaglandin concentration. **RESULTS:** The number (mean \pm SD) of gastric erosions seen with the ASA/PC formulation was significantly less than when ASA was used alone (8.7 \pm 10.7 vs 2.9 \pm 4.3; $p < 0.025$). A similar trend was seen in the duodenum but the difference was statistically not significant. The antral mucosal COX activity, as well as the level of prostaglandin 6-keto PGF1 α , were reduced significantly (80-88%) and to a similar extent by both ASA and ASA/PC. **CONCLUSIONS:** The present study shows that acute aspirin-induced damage to the gastric mucosa can be reduced by chemically associating ASA with PC. The mechanism of mucosal protection provided by this compound is not related to any alteration in the ability of ASA to inhibit mucosal COX activity. We believe this protection is attributable to the maintenance of the defensive hydrophobic barrier of the gastric mucosa.

Effects of green tea catechins on membrane fluidity.

Tsuchiya H. *Pharmacology* 1999;59:34-44.

Catechins originating from green tea have been used in plaque inhibition for caries prevention and treatment for liver damage because of their antibacterial activity against cariogenic bacteria and protective activity on hepatic cells. The effects of catechins on membrane fluidity were studied by a fluorescence polarization method using liposomes prepared with dipalmitoylphosphatidylcholine and dioleoylphosphatidylcholine to assess their pharmacological mechanism at micromol/l levels found in human body fluids after clinical application. All eight catechins tested, ranging from 1 to 1,000 micromol/l, significantly reduced membrane fluidity in both hydrophilic and hydrophobic regions of lipid bilayers. Catechin gallate esters were superior in fluidity reduction to the corresponding nonesters. The fluidity-reducing degree was different between the cis and trans forms, suggesting the stereospecific activity of catechins. A reference antiplaque agent, chlorhexidine, similarly reduced membrane fluidity at the antibacterial concentration. (+)-Catechin (250 micromol/l) and (-)-epigallocatechin gallate (2.5 micromol/l) significantly prevented the membrane fluidization induced by hepatotoxic chloroform. These results indicate that the reduction in membrane fluidity is responsible for the antiplaque and hepatoprotective effects of green tea catechins.

Plasma total homocysteine response to oral doses of folic acid and pyridoxine hydrochloride (vitamin B6) in healthy individuals. Oral doses of vitamin B6 reduce concentrations of serum folate.

Mansoor MA, Kristensen O, Hervig T, et al. *Scand J Clin Lab Invest* 1999;59:139-146.

Plasma total homocysteine response was compared in four groups of healthy individuals given orally divided doses of vitamin supplementations for a duration of 5 weeks. The vitamin supplements; A, 0.3 mg folic acid; B, 120 mg vitamin B6; C, combination of 0.3 mg folic acid and 120 mg vitamin B6 or D, 0.6 mg folic acid reduced the concentrations of plasma total homocysteine 20, 17, 32 and 24%, respectively. However, the intergroup comparisons did not show a significant difference in the effects of vitamin supplements. Multivariate analysis with correction for differences in pre-supplement values indicated a significant effect of vitamin B6 supplementation on plasma total homocysteine and serum folate. Our data show that plasma total homocysteine concentrations are reduced with low to medium divided doses of folic acid alone or in combination with vitamin B6.

Effects of coenzyme Q10 on myocardial protection during cardiac valve replacement and scavenging free radical activity in vitro.

Zhou M, Zhi Q, Tang Y, et al. *J Cardiovasc Surg* 1999;40:355-361.

BACKGROUND: To evaluate the effects of CoQ10 on myocardial protection in patients undergoing cardiac valve replacement and direct scavenging free radicals activity in vitro. **METHODS:** Twenty-four patients were randomly divided into two groups. Twelve patients in the CoQ10 group received intravenous and intracoronary CoQ10-treated “round the operative period”. Twelve patients in the control group received no CoQ10-treatment. **MEASURES:** Plasma malondialdehyde (MDA) concentration, erythrocyte superoxide dismutase (SOD) activity, and serum cardiac isoenzyme of creatine kinase (CK-MB) were measured in the perioperative and postoperative period. The effects of CoQ10 direct scavenging free radicals were determined with electron spin resonance (ESR) and spin-trapping techniques by an in vitro study. **RESULTS:** Plasma MDA concentration and serum CK-MB levels in the CoQ10 group were significantly lower than those in the control group. Erythrocyte SOD activity in the CoQ10 group was significantly higher than that in the control group. CoQ10 showed an obvious hydroxyl radical scavenging activity, but it could not scavenge superoxide anion radicals. **CONCLUSIONS:** These findings demonstrated that the use of intravenous and intracoronary CoQ10-treatment may play a more beneficial protective role during cardiac valve replacement through its antioxidant properties and membrane stabilization, as well as through its ability to scavenge hydroxyl radicals directly.

Chemoprevention of rat prostate carcinogenesis by early and delayed administration of dehydroepiandrosterone.

Rao KV, Johnson WD, Bosland MC, et al. *Cancer Res* 1999;59:3084-3089.

Two in vivo bioassays were conducted to evaluate the efficacy of dehydroepiandrosterone (DHEA) as an inhibitor of prostate carcinogenesis in rats. Prostate adenocarcinomas were induced in male Wistar-Unilever rats by a sequential regimen of cyproterone acetate and testosterone propionate, followed by a single i.v. injection of N-methyl-N-nitrosourea (MNU) and chronic androgen stimulation. In the first experiment, DHEA (1000 or 2000 mg/kg diet) was administered continuously to rats beginning 1 week before MNU exposure. In the second experiment, continuous administration of DHEA (2000 mg/kg diet) was begun either 1 week before, 20 weeks after, or 40 weeks after MNU exposure. Controls received basal diet without added DHEA. Studies were terminated at 13 months after MNU administration, and prostate cancer incidence was determined by histopathological evaluation of step sections of accessory sex glands. In the first study, continuous dietary administration of DHEA beginning 1 week before MNU resulted in a dose-related inhibition of prostate cancer induction. In the second experiment, comparable reductions in prostate cancer incidence were observed in groups exposed to DHEA beginning 1 week before, 20 weeks after, and 40 weeks after carcinogen exposure. These data demonstrate that nontoxic doses of DHEA confer significant protection against prostate carcinogenesis in rats. The efficacy of delayed administration of DHEA suggests that the compound confers protection against later stages of prostate cancer induction and can suppress the progression of existing preneoplastic lesions to invasive disease.

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Dehydroepiandrosterone restores immune function following trauma-haemorrhage by a direct effect on T lymphocytes.

Catania RA, Angele MK, Ayala A, et al. *Cytokine* 1999;11:443-450.

Although a profound depression in immune function occurs following injury, the mechanism responsible for this is not fully understood. Furthermore, steroid hormones are known to be important mediators in the regulation of immune function. Although dehydroepiandrosterone (DHEA), the most plentiful steroid hormone, has been shown to stimulate immune function in normal animals, it is unknown whether DHEA has any salutary or detrimental effects on immune responses after trauma and haemorrhage. To study this, male mice were subjected to trauma, haemorrhage and resuscitation, following which they received either DHEA or vehicle subcutaneously. DHEA administration restored the normally depressed splenocyte proliferation as well as interleukin 2, interleukin 3, and interferon gamma elaboration following trauma and haemorrhage. In an attempt to determine the mechanisms mediating this effect, T cells were stimulated in vitro in the presence of DHEA and a variety of hormone antagonists. The stimulatory effect of DHEA on splenocyte proliferation was unaltered by the testosterone receptor antagonist flutamide, while the oestrogen antagonist tamoxifen completely abrogated its effect. In addition, DHEA administration normalized the elevated serum corticosterone level typically seen following injury. These results indicate, therefore, that DHEA improves splenocyte function after trauma and haemorrhage by directly stimulating T cells and also by preventing a rise in serum corticosterone. Copyright 1999 Academic Press.

The effect of alpha-tocopherol and beta-carotene supplementation on colorectal adenomas in middle-aged male smokers.

Malila N, Virtamo J, Virtanen M, et al. *Cancer Epidemiol Biomarkers Prev* 1999;8:489-493.

Epidemiological and experimental studies have indicated that dietary factors such as vitamin C, vitamin E, and beta-carotene are associated with the risk of colorectal cancer. This study was carried out within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study), whose participants were randomly assigned to four supplementation groups: (a) alpha-tocopherol (AT), 50 mg/day; (b) beta-carotene (BC), 20 mg/day; (c) both AT and BC; and (d) placebo. We included the 15,538 ATBC Study participants who had been randomized within the areas of three major cities in southern Finland. Cases of colorectal adenoma (n = 146) were identified by the pathology laboratories in the study areas, and these participants' medical records were collected and reviewed. Alpha-tocopherol supplementation increased the risk for adenomas (relative risk, 1.66; 95% confidence interval, 1.19-2.32), whereas beta-carotene supplementation had no effect on the risk (relative risk, 0.98; 95% confidence interval, 0.71-1.35). Slightly more prediagnosis rectal bleeding and intestinal pain occurred in those adenoma cases who received alpha-tocopherol supplements than in those who did not. Thus, some bias may have resulted, with alpha-tocopherol supplementation leading to more colonoscopies and, thus, to an increased detection of incident polyps in this group. This is further supported by the trial finding that alpha-tocopherol supplementation did not increase the risk of colorectal cancer.

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Vitamins A, C and E and the risk of breast cancer: results from a case-control study in Greece.

Bohlke K, Spiegelman D, Trichopoulos A, et al. *Br J Cancer* 1999;79:23-29.

Although several dietary compounds are hypothesized to have anticarcinogenic properties, the role of specific micronutrients in the development of breast cancer remains unclear. To address this issue, we assessed intake of retinol, beta-carotene, vitamin C and vitamin E in relation to breast cancer risk in a case-control study in Greece. Eight hundred and twenty women with histologically confirmed breast cancer were compared with 1548 control women. Dietary data were collected through a 115-item semiquantitative food frequency questionnaire. Data were modelled by logistic regression, with adjustment for total energy intake and established breast cancer risk factors, as well as mutual adjustment among the micronutrients. Among postmenopausal women, there was no association between any of the micronutrients evaluated and risk of breast cancer. Among premenopausal women, beta-carotene, vitamin C and vitamin E were each inversely associated with breast cancer risk, but after mutual adjustment among the three nutrients only beta-carotene remained significant; the odds ratio (OR) for a one-quintile increase in beta-carotene intake was 0.84 (95% confidence interval 0.73-0.97). The inverse association observed with beta-carotene intake, however, is slightly weaker than the association previously observed with vegetable intake in these data, raising the possibility that the observed beta-carotene effect is accounted for by another component of vegetables.

Association between iron deficiency and low-level lead poisoning in an urban primary care clinic.

Wright RO, Shannon MW, Wright RJ, Hu H. *Am J Public Health* 1999;89:1049-1053.

OBJECTIVES: The purpose of this study was to examine the association between iron deficiency and low-level lead poisoning. **METHODS:** Data were collected in an urban primary care clinic from 3650 children aged 9 to 48 months. Iron deficiency was defined as a red cell mean corpuscular volume (MCV) of less than 70 fL and a red cell distribution width (RDW) of more than 14.5 in children younger than 2 years, and an MCV of less than 73 fL and RDW of more than 14.5 in those 2 years or older. **RESULTS:** After adjustment for age, hemoglobin concentration, and insurance status, the odds ratios for iron deficiency predicting blood lead levels greater than or equal to 5 micrograms/dL and greater than or equal to 10 micrograms/dL were 1.63 (95% confidence interval [CI] = 1.29, 2.04) and 1.44 (95% CI = 1.004, 2.05). **CONCLUSIONS:** Iron deficiency is significantly associated with low-level lead poisoning in children aged 9 to 48 months.

Nutrient intake and use of beverages and the risk of kidney stones among male smokers.

Hirvonen T, Pietinen P, Virtanen M, et al. *Am J Epidemiol* 1999;150:187-194.

High intakes of calcium, potassium, and fluids have been shown to be associated with lowered risk of kidney stones. The authors studied the associations between diet and risk of kidney stones in a cohort of 27,001 Finnish male smokers aged 50-69 years who were initially free of kidney stones. All men participated in the Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study and completed a validated dietary questionnaire at baseline. After 5 years of follow-up (1985-1988), 329 men had been diagnosed with kidney stones. After data were controlled for possible confounders, the relative risk of kidney stones for men in the highest quartile of magnesium intake was 0.52 (95% confidence interval (CI) 0.32-0.85) as compared with men in the lowest quartile. Intake of fiber was directly associated with risk (relative risk (RR) = 2.06, 95% CI 1.39-3.03). Calcium intake was not associated with the risk of kidney stones. Beer consumption was inversely associated with risk of kidney stones; each bottle of beer consumed per day was estimated to reduce risk by 40% (RR = 0.60, 95% CI 0.47-0.76). In conclusion, the authors observed that magnesium intake and beer consumption were inversely associated and fiber intake was directly associated with risk of kidney stones.

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Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate.

Deal CL, Moskowitz RW.
Rheum Dis Clin North Am
1999;25:379-395.

There are a sufficient number of short-term studies with these agents suggesting efficacy equal to that seen in the symptomatic treatment of OA using NSAIDs. Two recent meta-analyses by McAlindon and colleagues and Towheed et al reviewed clinical trials of glucosamine and chondroitin in the treatment of osteoarthritis. The study by McAlindon and co-workers included all double-blind placebo-controlled trials of greater than 4 weeks' duration, testing oral or parenteral glucosamine or chondroitin for treatment of hip or knee osteoarthritis. Thirteen trials (six with glucosamine, seven with chondroitin) met eligibility criteria. The authors used global pain score or the Lequesne index in the index joint as the primary outcome measure and considered the trial positive if improvement in the treatment group was equal to or greater than 25% compared with the placebo group,

and was significant ($P < \text{or} = .05$). All 13 studies reviewed were classified as positive, demonstrating large effects, compared with placebo (39.5% [S.D. 21.9] for glucosamine, 40.2% [S.D. 6.4] for chondroitin). The authors concluded that clinical trials of these two agents showed substantial benefit in the treatment of osteoarthritis but provided insufficient information about study design and conduct to allow definitive evaluation. Towheed and colleagues reviewed nine randomized, controlled trials of glucosamine sulfate in osteoarthritis. In seven of the randomized controlled trials, in which they compared glucosamine with placebo, glucosamine was always superior. In two randomized controlled trials comparing glucosamine to ibuprofen, glucosamine was superior in one and equivalent in one. Methodologic problems, including lack of standardized case definition of osteoarthritis and lack of standardized outcome assessment led the authors to conclude that further studies are needed to determine if route of administration is important and whether the therapeutic effect is site specific. A meta-analysis of chondroitin sulfate trials has also been published. Of the 12 published trials, 4 randomized double-blind placebo or NSAID-controlled trials with 227 patients on chondroitin sulfate were entered into the analysis. All four studies showed chondroitin sulfate to be superior to placebo, with respect to Lequesne index, visual analog scale for pain and medication consumption. Significant changes ($P < \text{or} = .05$) were seen in those treated from day 60 to the study endpoints (150 to 180 days). Pooled data demonstrated at least 50% improvement in the study variables in the chondroitin treated group. Discrepancies in some of the study findings reported in the literature may relate to the composition of the nutritional supplements used. Studies in the United States have revealed that a number of preparations claiming to contain certain doses of glucosamine or chondroitin sulfate have significantly less (or none) of the dosages described. Accordingly, it is essential that studies performed with these agents use preparations that are carefully defined in manufacture. The amounts generally administered are glucosamine, 1500 mg, and chondroitin sulfate, 1200 mg, daily. Although glucosamine has been described as effective when used alone, it is probably reasonable to use the combination pending further studies. The average cost is approximately \$30 to \$45 per month. In the interim, what should physicians tell their patients when they ask whether these agents are effective, or whether they should or should not take them? The authors emphasize that these agents are not FDA-evaluated or recommended for the treatment of OA. They are available as health food supplements, and the number of studies of toxicity, particularly with respect to long-term evaluations, is limited. The pros and cons of these agents and the published data are described so that patients can make a reasonably informed decision as to whether they wish to proceed with use of these agents in therapy. (ABSTRACT TRUNCATED)