

ABSTRACTS

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Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration.

Fourteen American Cocker Spaniels (ACS) with dilated cardiomyopathy (DCM) were studied to determine if individuals of this breed with DCM are systemically taurine- or carnitine-deficient and to determine if they are responsive to taurine and carnitine supplementation. American Cocker Spaniels with DCM were identified using echocardiography, and plasma was analyzed for taurine and carnitine concentrations. Each dog was randomly assigned to receive either taurine and carnitine supplementation or placebo. Echocardiograms and clinical examinations were repeated monthly for 4 months. During this period, the investigators and owners were blinded with respect to the treatment being administered. Each dog was weaned off its cardiovascular drugs (furosemide, digoxin, and an angiotensin converting enzyme inhibitor) if an echocardiographic response was identified. At the 4-month time period, each investigator was asked to decide whether he or she thought his or her patient was receiving placebo or taurine/carnitine, based on presence or absence of clinical and echocardiographic improvement. Unblinding then occurred, and dogs receiving placebos were switched to taurine and carnitine supplementation and followed monthly for 4 additional months. All dogs were reexamined 6 months after starting supplementation; survival time and cause of death were recorded for each dog. Data from 3 dogs were not included because of multiple protocol violations. Each dog had a plasma taurine concentration < 50 nmol/mL (mean \pm SD for the group 15 ± 17 nmol/mL) at baseline; normal range, 50-180 nmol/mL. The plasma taurine concentration did not exceed 50 nmol/mL at any time in the dogs receiving placebo ($n = 5$), but increased to 357 ± 157 nmol/mL (range 140-621 nmol/mL) during taurine and carnitine supplementation ($n = 11$). Plasma carnitine concentration was within, only slightly below, or slightly above reported limits of normality at baseline (29 ± 15 μ mol/L); did not change during placebo administration; and increased significantly during supplementation (349 ± 119 μ mol/L; $n = 11$). Echocardiographic variables did not change during placebo administration. During supplementation, left ventricular end-diastolic and end-systolic diameters, and mitral valve E point-to-septal separation decreased significantly in both groups. Shortening fraction increased significantly but not into the normal range. Echocardiographic variables remained improved at 6 months. All dogs were successfully weaned off furosemide, an angiotensin converting enzyme inhibitor, and digoxin once an echocardiographic response was identified. Nine of the dogs have died since the onset of the study in 1992. One dog died of recurrence of DCM and heart failure 31 months after starting supplementation; six dogs died of noncardiac causes. Two dogs developed degenerative mitral valve disease and died of complications of this disease. Dogs less than 10 years of age lived for 46 ± 11 months, whereas dogs older than 10 years of age lived for 14 ± 7 months. Two of the 11 dogs were alive at the time of publication, having survived for 3.5 and 4.5 years, respectively. We conclude that ACS with DCM are taurine-deficient and are responsive to taurine and carnitine supplementation. Whereas myocardial function did not return to normal in most dogs, it did improve enough to allow discontinuation of cardiovascular drug therapy and to maintain a normal quality of life for months to years.

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Phytoestrogens and inhibition of angiogenesis.

The consumption of a plant-based diet can prevent the development and progression of chronic diseases associated with extensive neovascularization, including the progression and growth of solid malignant tumours. We have previously shown that the plant-derived isoflavonoid genistein is a potent inhibitor of cell proliferation and in vitro angiogenesis. Moreover, the concentration of genistein in the urine of subjects consuming a plant-based diet is 30-fold higher than that in subjects consuming a traditional Western diet. We have also reported that certain structurally related flavonoids are more potent inhibitors than genistein. Indeed, 3-hydroxyflavone, 3',4'-dihydroxyflavone, 2',3'-dihydroxyflavone, fisetin, apigenin and luteolin inhibit the proliferation of normal and tumour cells as well as in vitro angiogenesis at half-maximal concentrations in the lower micromolar range. The wide distribution of isoflavonoids and flavonoids in the plant kingdom, together with their anti-angiogenic and anti-mitotic properties, suggest that these phytoestrogens may contribute to the preventive effect of a plant-based diet on chronic diseases, including solid tumours.

Influence of selegiline and lipoic acid on the life expectancy of immunosuppressed mice.

Ten groups of 14 immunosuppressed NMRI-mice (nu/nu) were raised and kept under germ-reduced conditions. The control animals were fed a germ-reduced diet, nine other groups received the same diet with selegiline (CAS 14611-51-9, Deprenyl) or lipoic acid (thioctic acid, CAS 62-46-4) admixed at various amounts. The 50% survival rate, the total life span of each group and the areas under the curves were determined to evaluate life expectancy as compared to the controls. The racemate of lipoic acid at high dosage (350 mg/kg body weight) reduced the life span significantly. The S(-)-enantiomer of lipoic acid (75 mg/kg body weight) increased the 50% survival rate, whereas the physiologic R(+)-enantiomer (9 mg/kg body weight) expanded the total life span of its group. Alteration of only one out of three parameters was not considered significant. All other groups except for one did not differ from controls: only animals which obtained 75 micrograms selegiline per kg of body weight and per day exerted increased life expectancies by all three parameters. This group exhibited also in statistical evaluation a significantly ($p < 0.05$) prolonged survival time up to about 200% as compared to the control animals.

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Immunomodulatory effect of beta-carotene on T lymphocyte subsets in patients with resected colonic polyps and cancer.

Results from a number of studies suggest that beta-carotene-containing foods prevent the initiation or progression of various cancers. One possible mechanism for this effect could be enhancement of the immune response. The aim of this study was to determine whether beta-carotene modulates T lymphocyte subsets in patients affected with colonic polyps or cancerous lesions. Patients with previous adenomatous colonic polyps ($n = 18$) or colon cancers ($n = 19$) were randomized to receive placebo or beta-carotene (30 mg/day) for three months. Percentages of T lymphocyte subsets were determined using flow cytometry in blood samples collected before randomization and at three months. T lymphocyte subsets of 14 normal control subjects were also determined for comparison. Initially, there was no difference in total leukocyte counts, percentage of lymphocytes, and various subsets of lymphocytes among the three groups, although in cancer patients there was a lower percentage of CD4 and interleukin-2 (IL-2) receptor-positive (IL-2R+) cells than in patients with polyps and in controls. After supplementation with beta-carotene, a significant increase in IL-2R+ T lymphocytes (from 12.7 +/- 3.0% to 26.0 +/- 1.9%) and CD4+ lymphocytes (from 40.9 +/- 3.1% to 45.6 +/- 3.2%) was seen only in the cancer patients. These percentages remained unchanged in patients with adenomatous polyps receiving placebo or beta-carotene. We concluded that beta-carotene increased the number of IL-2R+ T lymphocytes and CD4+ lymphocytes, which in turn may produce IL-2 only in patients with cancer who may already have some deficiency in their immune system. This increase in activated T lymphocytes may mediate cytotoxic reactions to cancer cells via cytokine production.

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Modulated mitogenic proliferative responsiveness of lymphocytes in whole-blood cultures after a low-carotene diet and mixed-carotenoid supplementation in women.

To determine the effects of dietary carotenes on the mitogenic proliferative responsiveness of blood lymphocytes in vitro, nine premenopausal women were fed a low-carotene diet for 120 d. Low-dose beta-carotene (0.5 mg/d) was given to five subjects on days 1-60, while four received a placebo. All subjects received a low-dose beta-carotene (0.5 mg/d) supplement on days 61-120, plus a carotenoid complex on days 101-120. The mean (+/-SEM) serum beta-carotene concentration for the combined beta-carotene supplemented and placebo subjects ($n = 9$) was not significantly reduced from that on day 1 (1.27 +/- 0.24 $\mu\text{mol/L}$) on days 60 (0.66 +/- 0.14 $\mu\text{mol/L}$) and 100 (0.91 +/- 0.38 $\mu\text{mol/L}$), but on day 120 (3.39 +/- 0.44 $\mu\text{mol/L}$) it was increased above that on days 1, 60, and 100. Maximum mitogenic proliferative responsiveness of blood lymphocytes in vitro to optimal dose phytohemagglutinin (PHA) was reduced on days 60 ($P = 0.025$) and 100 ($P < 0.0001$), but corrected itself on day 120 to a value above those on day 1 ($P = 0.04$), day 60 ($P = 0.0001$), and day 100 ($P < 0.0001$). Present findings show that a diet low in carotene had a suppressive effect on the maximum mitogenic proliferative responsiveness of blood lymphocytes in vitro, which was not corrected with low-dose beta-carotene supplementation but was with a carotenoid complex from vegetables rich in carotenoids.

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Radioprotective effects of antioxidative plant flavonoids in mice.

Radioprotective effects of tea infusions and plant flavonoids were investigated by using the micronucleus test for anticlastogenic activity and the thiobarbituric acid assay for antioxidative activity. A single gastric intubation of rooibos tea (*Aspalathus linearis*) infusion at 1 ml per mouse 2 h prior to gamma-ray irradiation (1.5 Gy) reduced the frequency of micronucleated reticulocytes (MNRETs). After the fractionation of rooibos tea infusion, the flavonoid fraction was found to be most anticlastogenic and antioxidative. From this fraction, luteolin was isolated as an effective component. Then, anticlastogenic effects of 12 flavonoids containing luteolin and their antioxidative activities against lipid peroxidation by Fenton's reagent were examined. A good

correlation ($r=0.717$) was observed between both activities. Luteolin showed the most effective potency. A gastric intubation of luteolin (10 micromoles/kg) 2 h prior to gamma-ray irradiation (6 Gy) suppressed lipid peroxidation in mouse bone marrow and spleen and a trend of protective effect of luteolin against the decrease of endogenous ascorbic acid in mouse bone marrow after gamma-ray irradiation (3 Gy) was observed. These results suggest that plant flavonoids, which show antioxidative potency in vitro, work as antioxidants in vivo and their radioprotective effects may be attributed to their scavenging potency towards free radicals such as hydroxyl radicals. Therefore, the flavonoids contained in tea, vegetables and fruits seem to be important as antioxidants in the human diet.

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