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ABSTRACTS

Featured:

- Lycopene
- Antioxidants
- Vitamin B12

Lycopene and coronary heart disease

**Tomato lycopene and low density lipoprotein oxidation:
a human dietary intervention study**

Lipids 1998 Oct;33(10):981-4

Increase in low density lipoprotein (LDL) oxidation is hypothesized to be causally associated with increasing risk of atherosclerosis and coronary heart disease. In recent epidemiological studies, tissue and serum levels of lycopene, a carotenoid available from tomatoes, have been found to be inversely related to risk of coronary heart disease. A study was undertaken to investigate the effect of dietary supplementation of lycopene on LDL oxidation in 19 healthy human subjects. Dietary lycopene was provided using tomato juice, spaghetti sauce, and tomato oleoresin for a period of 1 wk each. Blood samples were collected at the end of each treatment. Serum lycopene was extracted and measured by high-performance liquid chromatography using an absorbance detector. Serum LDL was isolated by precipitation with buffered heparin, and thiobarbituric acid-reactive substances (TBARS) and conjugated dienes (CD) were measured to estimate LDL oxidation. Both methods, to measure LDL oxidation LDL-TBARS and LDL-CD, were in good agreement with each other. Dietary supplementation of lycopene significantly increased serum lycopene levels by at least twofold. Although there was no change in serum cholesterol levels (total, LDL, or high-density lipoprotein), serum lipid peroxidation and LDL oxidation were significantly decreased. These results may have relevance for decreasing the risk for coronary heart disease.

Vitamin and mineral supplementation may reduce cancer risk

Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence,

and disease-specific mortality in the general population.

J Natl Cancer Inst 1993 Sep 15;85(18):1483-92

BACKGROUND: Epidemiologic evidence indicates that diets high in fruits and vegetables are associated with a reduced risk of several cancers, including cancers of the esophagus and stomach. Vitamins and minerals in these foods may contribute to the reduced cancer risk. The people of Linxian County, China, have one of the world's highest rates of esophageal/gastric cardia cancer and a persistently low intake of several micronutrients. **PURPOSE:** We sought to determine if dietary supplementation with specific vitamins and minerals can lower mortality from or incidence of cancer as well as mortality from other diseases in Linxian. **METHODS:** Individuals of ages 40-69 were recruited in 1985 from four Linxian communes. Mortality and cancer incidence during March 1986-May 1991 were ascertained for 29,584 adults who received daily vitamin and mineral supplementation throughout this period. The subjects were randomly assigned to intervention groups according to a one-half replicate of a 2(4) factorial experimental design. This design enabled testing for the effects of four combinations of nutrients: (A) retinol and zinc; (B) riboflavin and niacin; (C) vitamin C and molybdenum; and (D) beta carotene, vitamin E, and selenium. Doses ranged from one to two times U.S. Recommended Daily Allowances. **RESULTS:** A total of 2127 deaths occurred among trial participants during the intervention period. Cancer was the leading cause of death, with 32% of all deaths due to esophageal or stomach cancer, followed by cerebrovascular disease (25%). Significantly ($P = .03$) lower total mortality (relative risk [RR] = 0.91; 95% confidence interval [CI] = 0.84-0.99) occurred among those receiving supplementation with beta carotene, vitamin E, and selenium. The reduction was mainly due to lower cancer rates (RR = 0.87; 95% CI = 0.75-1.00), especially stomach cancer (RR = 0.79; 95% CI = 0.64-0.99), with the reduced risk beginning to arise about 1-2 years after the start of supplementation with these vitamins and minerals. No significant effects on mortality rates from all causes were found for supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum. Patterns of cancer incidence, on the basis of 1298 cases, generally resembled those for cancer mortality. **CONCLUSIONS:** The findings indicate that vitamin and mineral supplementation of the diet of Linxian adults, particularly with the combination of beta carotene, vitamin E, and selenium, may effect a reduction in cancer risk in this population. **IMPLICATIONS:** The results on their own are not definitive, but the promising findings should stimulate further research to clarify the potential benefits of micronutrient supplements.

Lycopene works synergistically with
alpha-tocopherol

Lycopene in association with alpha-tocopherol inhibits at physiological concentrations proliferation of prostate carcinoma cells

Biochem Biophys Res Commun 1998 Sep 29;250(3):582-5

The effect of lycopene alone or in association with other antioxidants was studied on the growth of two different human prostate carcinoma cell lines (the androgen insensitive DU-145 and PC-3). It was found that lycopene alone was not a potent inhibitor of prostate carcinoma cell proliferation. However, the simultaneous addition of lycopene together with alpha-tocopherol, at physiological concentrations (less than 1 microM and 50 microM, respectively), resulted in a strong inhibitory effect of prostate carcinoma cell proliferation, which reached values close to 90 %. The effect of lycopene with alpha-tocopherol was synergistic and was not shared by beta-tocopherol, ascorbic acid and probucol.

Lycopene and lutein

Carotenoid mixtures protect multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein

FEBS Lett 1998 May 8;427(2):305-8

Antioxidant activity of carotenoids in multilamellar liposomes assayed by inhibition of formation of thiobarbituric acid-reactive substances was in the ranking: lycopene > alpha-tocopherol > alpha-carotene > beta-cryptoxanthin > zeaxanthin = beta-carotene > lutein. Mixtures of carotenoids were more effective than the single compounds. This synergistic effect was most pronounced when lycopene or lutein was present. The superior protection of mixtures may be related to specific positioning of different carotenoids in membranes.

Alzheimer's and blood levels of folate,
vitamin B12 and homocysteine

Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer's disease.

Arch Neurol 1998 Nov;55(11):1449-55

BACKGROUND: Recent studies suggest that vascular disease may contribute to the cause of Alzheimer's disease (AD). Since elevated plasma total homocysteine (tHcy) level is a risk factor for vascular disease, it may also be relevant to AD. **OBJECTIVE:** To examine the association of AD with blood levels of tHcy, and its biological determinants folate and vitamin B12. **DESIGN:** Case-control study of 164 patients, aged 55 years or older, with a clinical diagnosis of dementia of Alzheimer's type (DAT), including 76 patients with histologically confirmed AD and 108 control subjects. **SETTING:** Referral population to a hospital clinic between July 1988 and April 1996. **MAIN OUTCOME MEASURES:** Serum tHcy, folate, and vitamin B12 levels in patients and controls at entry; the odds ratio of DAT or confirmed AD with elevated tHcy or low vitamin levels; and the rate of disease progression in relation to tHcy levels at entry. **RESULTS:** Serum tHcy levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with DAT and patients with histologically confirmed AD than in controls. The odds ratio of confirmed AD associated with a tHcy level in the top third (≥ 14 micromol/L) compared with the bottom third (≤ 11 micromol/L) of the control distribution was 4.5 (95% confidence interval, 2.2-9.2), after adjustment for age, sex, social class, cigarette smoking, and apolipoprotein E epsilon4. The corresponding odds ratio for the lower third compared with the upper third of serum folate distribution was 3.3 (95% confidence interval, 1.8-6.3) and of vitamin B12 distribution was 4.3 (95% confidence interval, 2.1-8.8). The mean tHcy levels were unaltered by duration of symptoms before enrollment and were stable for several years afterward. In a 3-year follow-up of patients with DAT, radiological evidence of disease progression was greater among those with higher tHcy levels at entry. **CONCLUSIONS:** Low blood levels of folate and vitamin B12, and elevated tHcy levels were associated with AD. The stability of tHcy levels over time and lack of relationship with duration of symptoms argue against these findings being a consequence of disease and warrant further studies to assess the clinical relevance of these associations for AD.

Free radical reactions are ubiquitous in living things. Studies on the origin and evolution of life provide a reasonable explanation for the prominent presence of this unruly class of chemical reactions. These reactions have been implicated in aging. Aging is the accumulation of changes responsible for the sequential alterations that accompany advancing age, and the associated progressive increases in the chance of disease and death. Aging changes are attributed to the environment and disease, and to an inborn process, the aging process. The latter produces aging changes at an exponentially increasing rate with advancing age. Improvements in general living conditions decrease the chance of death toward limiting values. Chances for death are now near these limits in the developed countries. Future significant increases in the average life span in the developed countries can only be achieved by slowing the rate of damage produced by the aging process. Support for the possibility that free radical reactions are responsible for the aging process now includes: i) studies on the origin of life and evolution; ii) studies on the effect of ionising radiation on living things; iii) dietary manipulations of endogenous free radical reactions; iv) the plausible explanations it provides for aging phenomena; and v) the growing numbers of studies that implicate free radical reactions in the pathogenesis of specific diseases. It is reasonable to expect on the basis of present data, that the average life expectancy at birth can be increased by 5 or more years by nutritious low caloric diets supplemented with one or more free radical reaction inhibitors.

Flavonoids may reduce risk of death from heart disease

Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study.

Lancet 1993 Oct 23;342(8878):1007-11

Flavonoids are polyphenolic antioxidants naturally present in vegetables, fruits, and beverages such as tea and wine. In vitro, flavonoids inhibit oxidation of low-density lipoprotein and reduce thrombotic tendency, but their effects on atherosclerotic complications in human beings are unknown. We measured the content in various foods of the flavonoids quercetin, kaempferol, myricetin, apigenin, and luteolin. We then assessed the flavonoid intake of 805 men aged 65-84 years in 1985 by a cross-check dietary history; the men were then followed up for 5 years. Mean baseline flavonoid intake was 25.9 mg daily. The major sources of intake were tea (61%), onions (13%), and apples (10%). Between 1985 and 1990, 43 men died of coronary heart disease. Fatal or non-fatal myocardial infarction occurred in 38 of 693 men with no history of myocardial infarction at baseline. Flavonoid intake (analyzed in tertiles) was significantly inversely associated with mortality from coronary heart disease (p for trend = 0.015) and showed an inverse relation with incidence of myocardial infarction, which was of borderline significance (p for trend = 0.08). The relative risk of coronary heart disease mortality in the highest versus the lowest tertile of flavonoid intake was 0.42 (95% CI 0.20-0.88). After adjustment for age, body-mass index, smoking, serum total and high-density-lipoprotein cholesterol, blood pressure, physical activity, coffee consumption, and intake of energy, vitamin C, vitamin E, beta carotene, and dietary fibre, the risk was still significant (0.32 [0.15-0.71]). Intakes of tea, onions, and apples were also inversely related to coronary heart disease mortality, but these associations were weaker. Flavonoids in regularly consumed foods may reduce the risk of death from coronary heart disease in elderly men.

CoQ10 and AMI

Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction.

Cardiovasc Drugs Ther 1998 Sep;12(4):347-53

The effects of oral treatment with coenzyme Q10 (120 mg/d) were compared for 28 days in 73 (intervention group A) and 71 (placebo group B) patients with acute myocardial infarction (AMI). After treatment, angina pectoris (9.5 vs. 28.1), total arrhythmias (9.5% vs. 25.3%), and poor left ventricular function (8.2% vs. 22.5%) were significantly ($P < 0.05$) reduced in the coenzyme Q group than placebo group. Total cardiac events, including cardiac deaths and nonfatal infarction, were also significantly reduced in the coenzyme Q10 group compared with the placebo group (15.0% vs. 30.9%, $P < 0.02$). The extent of cardiac disease, elevation in cardiac enzymes, and oxidative stress at entry to the study were comparable between the two groups. Lipid peroxides, diene conjugates, and malondialdehyde, which are indicators of oxidative stress, showed a greater reduction in the treatment group than in the placebo group. The antioxidants vitamin A, E, and C and beta-carotene, which were lower initially after AMI, increased more in the coenzyme Q10 group than in the placebo group. These findings suggest that coenzyme Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of the onset of symptoms. More studies in a larger number of patients and long-term follow-up are needed to confirm our results.

The effect of vitamin B12 deficiency on older veterans and its relationship to health

J Am Geriatr Soc 1998 Oct;46(10):1199-206

OBJECTIVE: To examine the effect of vitamin B12 deficiency on older veterans and its relationship to general health and cognitive impairment. **DESIGN:** Cross-sectional study. **SETTING:** Oklahoma City Veterans Affairs Medical Center. **PARTICIPANTS:** Data for this research were obtained from 303 ambulatory, older veterans who used the outpatient laboratories of the Oklahoma City Department of Veterans Affairs Medical Center. Subjects were included in the study if they were 65 years of age and older and if they had no known diagnosis associated with B12 deficiency. The sample in this study consisted of 301 men and 2 women aged 65 to 89 years. **MEASUREMENTS:** This study used two separate measurements of vitamin B12 deficiency: (1) a strict definition of B12 deficiency (serum B12 level < laboratory norm) and (2) a broader definition of B12 deficiency (serum B12 level < laboratory norm or laboratory norm < B12 < 300 pg/mL and methyl malonic acid (MMA) or homocysteine (HC) elevated by more than two standard deviations). The laboratory norm is 200 pg/mL. The dependent variables were measures of cognitive impairment and general health. Cognitive impairment was measured using the Folstein Mini-Mental State Examination (MMSE) and general health was measured using the RAND 36-Item Health Survey Version 1.0. The control variables for this study were the subjects' daily alcohol intake, daily intake of a vitamin/mineral supplement, annual income, and level of education.

RESULTS/CONCLUSIONS: Nineteen subjects (6%) were vitamin B12-deficient as measured by the strict definition of B12 deficiency (serum B12 level < laboratory norm), and 49 subjects (16%) were vitamin B12-deficient as measured by the broader definition of B12 deficiency (serum B12 level < laboratory norm or laboratory norm < B12 < 300 pg/mL and MMA or HC elevated by more than two standard deviations). Vitamin B12 level decreases as age increases. Of the nine general health outcomes measured by using the RAND 36-Item Health Survey, only bodily pain is associated with vitamin B12 deficiency, and only then when B12 deficiency is measured as serum B12 level < laboratory norm, the strict definition of B12 deficiency. Vitamin B12-deficient subjects experience more bodily pain than those with normal vitamin B12 levels. There is a significant difference between B12-deficient subjects and B12 normal subjects on cognitive impairment, with B12 normal subjects indicating less cognitive impairment, only when B12 deficiency is measured as B12 level < laboratory norm, the strict definition of B12 deficiency. The broader measurement of vitamin B12 deficiency (i.e., serum B12 level < laboratory norm or laboratory norm < B12 < 300 pg/mL and MMA or HC elevated by more than two standard deviations) is not a significant correlate of cognitive impairment and general health.

B 12 and light sensitivity

Effects of vitamin B12 on plasma melatonin rhythm in humans: increased light sensitivity phase-advances the circadian clock?

Experientia 1992 Aug 15;48(8):716-20

Vitamin B12 (methylcobalamin) was administered orally (3 mg/day) to 9 healthy subjects for 4 weeks. Nocturnal melatonin levels after exposure to bright light (ca. 2500 lx) were determined, as well as the levels of plasma melatonin over 24 h. The timing of sleep was also recorded. Vitamin B12 was given blind to the subjects and crossed over with placebo. We found that the 24-h melatonin rhythm was significantly phase-advanced (1.1 h) in the vitamin B12 trial as compared with that in the placebo trial. In addition, the 24-h mean of plasma melatonin level was much lower in the vitamin B12 trial than with the placebo. Furthermore, the nocturnal melatonin levels during bright light exposure were significantly lower in the vitamin B12 trial than with the placebo. On the other hand, vitamin B12 did not affect the timing of sleep. These findings raise the possibility that vitamin B12 phase-advances the human circadian rhythm by increasing the light sensitivity of the circadian clock.

Oral cobalamin therapy

Effective treatment of cobalamin deficiency with oral cobalamin

Blood 1998 Aug 15;92(4):1191-8

Because cobalamin deficiency is routinely treated with parenteral cobalamin, we investigated the efficacy of oral therapy. We randomly assigned 38 newly diagnosed cobalamin deficient patients to receive cyanocobalamin as either 1 mg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 or 2 mg orally on a daily basis for 120 days. Therapeutic effectiveness was evaluated by measuring hematologic and neurologic improvement and changes in serum levels of cobalamin (normal, 200 to 900 pg/mL) methylmalonic acid (normal, 73 to 271 nmol/L), and homocysteine (normal, 5.1 to 13.9 micromol/L). Five patients were subsequently found to have folate deficiency, which left 18 evaluable patients in the oral group and 15 in the parenteral group. Correction of hematologic and neurologic abnormalities was prompt and indistinguishable between the 2 groups. The mean pretreatment values for serum cobalamin, methylmalonic acid, and homocysteine were, respectively, 93 pg/mL, 3,850 nmol/L, and 37.2 micromol/L in the oral group and 95 pg/mL, 3,630 nmol/L, and 40.0 micromol/L in the parenteral therapy group. After 4 months of therapy, the respective mean values were 1,005 pg/mL, 169 nmol/L, and 10.6 micromol/L in the oral group and 325 pg/mL, 265 nmol/L, and 12.2 micromol/L in the parenteral group. The higher serum cobalamin and lower serum methylmalonic acid levels at 4 months posttreatment in the oral group versus the parenteral group were significant, with $P < .0005$ and $P < .05$, respectively. In cobalamin deficiency, 2 mg of cyanocobalamin administered orally on a daily basis was as effective as 1 mg administered intramuscularly on a monthly basis and may be superior.

Methyl-B12 may benefit patients with peripheral neuropathies

Ultra-high dose methylcobalamin promotes nerve regeneration in experimental acrylamide neuropathy

J Neurol Sci 1994 Apr;122(2):140-3

Despite intensive searches for therapeutic agents, few substances have been convincingly shown to enhance nerve regeneration in patients with peripheral neuropathies. Recent biochemical evidence suggests that an ultra-high dose of methylcobalamin (methyl-B12) may up-regulate gene transcription and thereby protein synthesis. We examined the effects of ultra-high dose of methyl-B12 on the rate of nerve regeneration in rats with acrylamide neuropathy, using the amplitudes of compound muscle action potentials (CMAPs) after tibial nerve stimulation as an index of the number of regenerating motor fibers. After intoxication with acrylamide, all the rats showed equally decreased CMAP amplitudes. The animals were then divided into 3 groups; rats treated with ultra-high (500 micrograms/kg body weight, intraperitoneally) and low (50 micrograms/kg) doses of methyl-B12, and saline-treated control rats. Those treated with ultra-high dose showed significantly faster CMAP recovery than saline-treated control rats, whereas the low-dose group showed no difference from the control. Morphometric analysis revealed a similar difference in fiber density between these groups. Ultra-high doses of methyl-B12 may be of clinical use for patients with peripheral neuropathies.

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