

LE Magazine January 2003

ABSTRACTS

CoQ10

Perspectives on therapy of cardiovascular diseases with coenzyme Q10 (ubiquinone).

A defective myocardial energy supply-due to lack of substrates and/or essential cofactors and a poor utilization efficiency of oxygen-may be a common final pathway in the progression of myocardial diseases of various etiologies. The vitamin-like essential substance coenzyme Q10, or ubiquinone, is a natural antioxidant and has a key role in oxidative phosphorylation. A biochemical rationale for using coenzyme Q10 as a therapy in heart disease was established years ago by Folkers and associates; however, this has been further strengthened by investigations of viable myocardial tissue from the author's series of 45 patients with various cardiomyopathies. Myocardial tissue levels of coenzyme Q10 determined by high-performance lipid chromatography were found to be significantly lower in patients with more advanced heart failure compared with those in the milder stages of heart failure. Furthermore, the myocardial tissue coenzyme Q10 deficiency might be restored significantly by oral supplementation in selected cases. In the author's open clinical protocol study with coenzyme Q10 therapy (100 mg daily) nearly two-thirds of patients revealed clinical improvement, most pronounced in those with dilated cardiomyopathy. Double-blind placebo-controlled trials have definitely confirmed that coenzyme Q10 has a place as adjunctive treatment in heart failure with beneficial effects on the clinical outcome, the patients' physical activity, and their quality of life. The positive results have been above and beyond the clinical status obtained from treatment with traditional principles-including angiotensin-converting enzyme inhibitors.

Clin Investig 1993;71(8 Suppl):S116-23

Isolated diastolic dysfunction of the myocardium and its response to CoQ10 treatment.

Symptoms of fatigue and activity impairment, atypical precordial pain and cardiac arrhythmia frequently precede by years the development of congestive heart failure. Of 115 patients with these symptoms, 60 were diagnosed as having hypertensive cardiovascular disease, 27 mitral valve prolapse syndrome, and 28 chronic fatigue syndrome. These symptoms are common with diastolic dysfunction, and diastolic function is energy dependent. All patients had blood pressure, clinical status, coenzyme Q10 (CoQ10) blood levels and echocardiographic measurement of diastolic function, systolic function and myocardial thickness recorded before and after CoQ10 replacement. At control, 63 patients were functional class III and 54 class II; all showed diastolic dysfunction; the mean CoQ10 blood level was 0.855 micrograms/ml; 65%, 15% and 7% showed significant myocardial hypertrophy, and 87%, 30% and 11% had elevated blood pressure readings in hypertensive disease, mitral valve prolapse and chronic fatigue syndrome, respectively. Except for higher blood pressure levels and more myocardial thickening in the hypertensive patients, there was little difference between the three groups. CoQ10 administration resulted in improvement in all; reduction in high blood pressure in 80%, and improvement in diastolic function in all patients with follow-up echocardiograms to date; a reduction in myocardial thickness in 53% of hypertensives and 36% of the combined prolapse and fatigue syndrome groups; and a reduced fractional shortening in those high at control and an increase in those initially low.

Clin Investig 1993;71(8 Suppl):S140-4

Pronounced increase of survival of patients with cardiomyopathy when treated with coenzyme Q10 and conventional therapy.

During 1982 to 1986, 43/137 patients with cardiomyopathy, Classes II, III and IV, had ejection fractions (EF) below 40%, and a mean EF of 25.1 +/- 10.3%. During treatment of these 43 patients with coenzyme Q10 (CoQ10), EF increased to 41.6 +/- 14.3% (p less than 0.001) over a mean period of three months (range, two to four months). At four subsequent periods up to 36 months EF ranged from 43.1 +/- 13.3 to 49.7 +/- 6.4% (each period, p less than 0.001). The mean CoQ10 control blood level was 0.85 +/- 0.26 micrograms/ml, which increased on treatment to 1.7 to 2.3 micrograms/ml for five periods up to 36 months (each period, p less than 0.001). The survival rates for all 137 patients treated with CoQ10 and for the 43 patients with EF below 40% were both about 75%/46 months. These two survival rates were comparable between 24 and 46 months, which is of extraordinary significance and importance when compared to survival of about 25%/36 months for 182 patients with EF below 46% on conventional therapy without CoQ10. The improved cardiac function and pronounced increase of survival show that therapy with CoQ10 is remarkably beneficial due to correction of CoQ10 deficiency in mechanisms of bioenergetics.

Int J Tissue React 1990;12(3):163-8

Skin aging

Low molecular weight antioxidants and their role in skin aging.

There is increasing evidence that reactive oxygen species play a pivotal role in the process of aging. The skin, as the outermost barrier of the body, is exposed to various exogenous sources of oxidative stress, in particular UV-irradiation. These are believed to be responsible for the extrinsic type of skin aging, termed photo-aging. It therefore seems reasonable to try to increase levels of protective low molecular weight antioxidants through a diet rich in fruits and vegetables or by direct topical application. Indeed, various in vitro and animal studies have proved that low molecular weight antioxidants, especially vitamins C and E, ascorbate and tocopherol, as well as lipoic acid, exert protective effects against oxidative stress. However, controlled long-term studies on the efficacy of low molecular weight antioxidants in the prevention or treatment of skin aging in humans are still lacking.

Clin Exp Dermatol 2001 Oct;26(7):578-82

Photoaging is associated with protein oxidation in human skin in vivo.

There is increasing evidence for the generation of reactive oxygen species in skin upon ultraviolet exposure, but little is known about their pathophysiologic relevance in human skin in vivo. We hypothesized that chronic and acute photodamage is mediated by depleted antioxidant enzyme expression and increased oxidative protein modifications. Biopsies from patients with histologically confirmed solar elastosis, from non-ultraviolet-exposed sites of age-matched controls, and from young subjects were analyzed. To evaluate the influence of acute ultraviolet exposures, buttock skin of 12 healthy subjects was irradiated repetitively on 10 d with a solar simulator and compared intra-individually to non-ultraviolet-treated contralateral sites. The antioxidant enzymes catalase, copper-zinc superoxide dismutase and manganese superoxide dismutase were investigated by immunohistochemistry. Protein carbonyls were analyzed by immunohistochemical and immunoblotting techniques in human skin and in cell models. Whereas overall expression of antioxidant enzymes was very high in the epidermis, low baseline levels were found in the dermis. In photoaged skin, a significant depletion of antioxidant enzyme expression was observed within the stratum corneum and in the epidermis. Importantly, an accumulation of oxidatively modified proteins was found specifically within the upper dermis of photoaged skin. Upon acute ultraviolet exposure of healthy subjects, depleted catalase expression and increased protein oxidation were detected. Exposures of keratinocytes and fibroblasts to ultraviolet B, ultraviolet A and H₂O₂ led to dose-dependent protein oxidation and thus confirmed in vivo results. In conclusion, the correlation between photodamage and protein oxidation was demonstrated for the first time, which hence may be a relevant pathophysiologic factor in photoaging.

J Invest Dermatol 2002 Apr;118(4):618-25

Double-blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage.

BACKGROUND: Aging of the population, in particular the "baby boomers," has resulted in increased interest in methods of reversal of photodamage. Non-invasive treatments are in high demand, and our knowledge of mechanisms of photodamage to skin, protection of the skin and repair of photodamage are becoming more sophisticated and complex. **OBJECTIVE:** The objective of this study is to determine if the topical use of a vitamin C preparation can stimulate the skin to repair photodamage and result in clinically visible differences, as well as microscopically visible improvement. **METHODS:** Ten patients applied in a double-blind manner a newly formulated vitamin C complex having 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (lipid soluble) in an anhydrous polysilicone gel base to one-half of the face and the inactive polysilicone gel base to the opposite side. Clinical evaluation of wrinkling, pigmentation, inflammation and hydration was performed prior to the study and at weeks 4, 8 and 12. Two mm punch biopsies of the lateral cheeks were performed at 12 weeks in four patients and stained with hematoxylin and eosin, as well as in situ hybridization studies using an anti-sense probe for mRNA for type I collagen. A questionnaire was also completed by each patient. **RESULTS:** A statistically significant improvement of the vitamin C-treated side was seen in the decreased photoaging scores of the cheeks ($P = 0.006$) and the peri-oral area ($P = 0.01$). The peri-orbital area improved bilaterally, probably indicating improved hydration. The overall facial improvement of the vitamin C side was statistically significant ($P = 0.01$). Biopsies showed increased Grenz zone collagen, as well as increased staining for mRNA for type I collagen. No patients were found to have any evidence of inflammation. Hydration was improved bilaterally. Four patients felt that the vitamin C-treated side improved unilaterally. No patient felt the placebo side showed unilateral improvement. **CONCLUSION:** This formulation of vitamin C results in clinically visible and statistically significant improvement in wrinkling when used topically for 12 weeks. This clinical improvement correlates with biopsy evidence of new collagen formation.

Dermatol Surg 2002 Mar;28(3):231-6

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ABSTRACTS

Quercetin

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

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 to 84 years in 1985 by a cross-check dietary history; the men were then followed up for five 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 (analysed 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.

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

Quercetin inhibits Shc- and phosphatidylinositol 3-kinase-mediated c-Jun N-terminal kinase activation by angiotensin II in cultured rat aortic smooth muscle cells.

Angiotensin II (Ang II) induces vascular smooth muscle cell (VSMC) hypertrophy, which results in various cardiovascular diseases. Ang II-induced cellular events have been implicated, in part, in the activation of mitogen-activated protein (MAP) kinases. Although it has been proposed that daily intake of bioflavonoids belonging to polyphenols reduces the incidence of ischemic heart diseases (known as "French paradox"), the precise mechanisms of efficacy have not been elucidated. Thus, we hypothesized that bioflavonoids may affect Ang II-induced MAP kinase activation in cultured rat aortic smooth muscle cells (RASMC). Our findings showed that Ang II stimulated rapid and significant activation of extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), and p38 in RASMC. Ang II-induced JNK activation was inhibited by 3,3',4',5,7-pentahydroxyflavone (quercetin), a major bioflavonoid in foods of plant origin, whereas ERK1/2 and p38 activation by Ang II were not affected by quercetin. Ang II caused a rapid tyrosine phosphorylation of Src homology and collagen (Shc), which was inhibited by quercetin. Quercetin also inhibited Ang II-induced Shc.p85 association and subsequent activation of phosphatidylinositol 3-kinase (PI3-K)/Akt pathway in RASMC. Furthermore, LY294002, a PI3-K inhibitor and a quercetin derivative, inhibited Ang II-induced JNK activation as well as Akt phosphorylation. Finally, Ang II-induced [(3)H]leucine incorporation was abolished by both quercetin and LY294002. These findings suggest that the preventing effect of quercetin on Ang II-induced VSMC hypertrophy are attributable, in part, to its inhibitory effect on Shc- and PI3-K-dependent JNK activation in VSMC. Thus, inhibition of JNK by quercetin may imply its usefulness for the treatment of cardiovascular diseases relevant to VSMC growth.

Mol Pharmacol 2001 Oct;60(4):656-65

Quercetin inhibits human vascular smooth muscle cell proliferation and migration.

BACKGROUND: The French paradox has been associated with regular intake of red wine, which is enriched with flavonoids. Quercetin, a flavonoid present in the human diet, exerts cardiovascular protection through its antioxidant properties. We hypothesized that the beneficial effect of quercetin also could be related to the inhibition of vascular smooth muscle cell proliferation and migration. **METHODS:** Human aortic smooth muscle cells (AoSMC) were grown in culture in the presence of serum. Quercetin inhibited the serum-induced proliferation of AoSMC. This inhibition was dose-dependent and not attributed to toxicity. Cell cycle analysis revealed that quercetin arrested AoSMC in the G(0)/G(1) phase. The effect of quercetin on AoSMC migration was examined using explant migration and Transwell migration assays. Quercetin significantly decreased migration in both assays in a consistent manner. Finally, Western blot analysis of AoSMC exposed to quercetin demonstrated a significant reduction in the activation of mitogen-activated protein kinase, a signaling pathway associated with the migration of vascular smooth muscle cells. **CONCLUSIONS:** Quercetin inhibits the proliferation and migration of AoSMC, concomitant with inhibition of mitogen-activated protein kinase phosphorylation. These findings provide new insights and a rationale for the potential use of quercetin in the

prophylaxis of cardiovascular diseases.

Surgery 2002 Feb;131(2):198-204

Carnosine

Carnosine protects against excitotoxic cell death independently of effects on reactive oxygen species.

The role of carnosine, N-acetylcarnosine and homocarnosine as scavengers of reactive oxygen species and protectors against neuronal cell death secondary to excitotoxic concentrations of kainate and N-methyl-D-aspartate was studied using acutely dissociated cerebellar granule cell neurons and flow cytometry. We find that carnosine, N-acetylcarnosine and homocarnosine at physiological concentrations are all potent in suppressing fluorescence of 2',7'-dichlorofluorescein, which reacts with intra-cellularly generated reactive oxygen species. However, only carnosine in the same concentration range was effective in preventing apoptotic neuronal cell death, studied using a combination of the DNA binding dye, propidium iodide, and a fluorescent derivative of the phosphatidylserine-binding dye, Annexin-V. Our results indicate that carnosine and related compounds are effective scavengers of reactive oxygen species generated by activation of ionotropic glutamate receptors, but that this action does not prevent excitotoxic cell death. Some other process, which is sensitive to carnosine but not the related compounds, is a critical factor in cell death. These observations indicate that at least in this system reactive oxygen species generation is not a major contributor to excitotoxic neuronal cell death.

Neuroscience 1999;94(2):571-7

Carnosine reacts with a glycated protein.

Oxidation and glycation induce formation of carbonyl (CO) groups in proteins, a characteristic of cellular aging. The dipeptide carnosine (beta-alanyl-L-histidine) is often found in long-lived mammalian tissues at relatively high concentrations (up to 20 mM). Previous studies show that carnosine reacts with low-molecular-weight aldehydes and ketones. We examine here the ability of carnosine to react with ovalbumin CO groups generated by treatment of the protein with methylglyoxal (MG). Incubation of MG-treated protein with carnosine accelerated a slow decline in CO groups as measured by dinitrophenylhydrazine reactivity. Incubation of [(14)C]-carnosine with MG-treated ovalbumin resulted in a radiolabeled precipitate on addition of trichloroacetic acid (TCA); this was not observed with control, untreated protein. The presence of lysine or N-(alpha)-acetylglycyl-lysine methyl ester caused a decrease in the TCA-precipitable radiolabel. Carnosine also inhibited cross-linking of the MG-treated ovalbumin to lysine and normal, untreated alpha-crystallin. We conclude that carnosine can react with protein CO groups (termed "carnosinylation") and thereby modulate their deleterious interaction with other polypeptides. It is proposed that, should similar reactions occur intracellularly, then carnosine's known "anti-aging" actions might, at least partially, be explained by the dipeptide facilitating the inactivation/removal of deleterious proteins bearing carbonyl groups.

Free Radic Biol Med 2000 May 15;28(10):1564-70

Carnosine prevents the activation of free-radical lipid oxidation during stress.

Carnosine (beta-alanyl-L-histidine) injected to intact albino rats (20 mg/kg body weight) induces depletion of lipid peroxidation (LPO) products in brain and blood serum, an increase of superoxide scavenging activity in brain and serum, decrease of cholesterol: phospholipid ratio and increase of easy oxidizable phospholipid portion in brain lipid extracts. After painful stress (footshock during two hours) LPO products are accumulated in brain and serum, cholesterol: phospholipid ratio increases and the portion of easy oxidizable phospholipids decreases. Carnosine given before stress prevents LPO activation. Effects of carnosine and stress are not additive: LPO inhibition induced by carnosine is much more in rats subjected to stress.

Biull Eksp Biol Med 1989 Feb;107(2):144-7

Vitamin Supplementation

Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer.

Ascorbic acid metabolism is associated with a number of mechanisms known to be involved in host resistance to malignant disease. Cancer patients are significantly depleted of ascorbic acid, and in our opinion this demonstrable biochemical characteristic indicates a substantially increased requirement and utilization of this substance to potentiate these various host resistance factors. The results of a clinical trial are presented in which 100 terminal cancer patients were given supplemental ascorbate as part of their routine management. Their progress is compared to that of 1000 similar patients treated identically, but who received no supplemental ascorbate. The mean survival time is more than 4.2 times as great for the ascorbate subjects (more than 210 days) as for the controls (50 days). Analysis of the survival-time curves indicates that deaths occur for about 90% of the ascorbate-treated

patients at one-third the rate for the controls and that the other 10% have a much greater survival time, averaging more than 20 times that for the controls. The results clearly indicate that this simple and safe form of medication is of definite value in the treatment of patients with advanced cancer.

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