

JOURNAL
ABSTRACTS

EECP

COMPARISON OF LONG-TERM RESULTS OF DRUG-ELUTING STENT AND BARE METAL STENT IMPLANTATION IN HEART TRANSPLANT RECIPIENTS WITH CORONARY ARTERY DISEASE.

The aim of the study was to compare long-term results of intracoronary implantation of drug-eluting stents (DES) and bare metal stents (BMS) in patients suffering from transplant coronary artery disease (TxCAD). MATERIAL AND METHODS: We performed a retrospective analysis of all intracoronary stent implantations for TxCAD among subjects with at least one follow-up coronary angiography. We identified 28 sirolimus-eluting DES (n = 17) patients, 24 BMS (n = 13 patients), and both DES and BMS (n = 7 patients) implantations among 23 recipients. Mean follow-up after DES was 14 months and after BMS implantation, 20 months. We compared the occurrence of in-stent restenosis (ISR), and patient survival in the context of risk factors that were identified separately for each stent type. Significance was assessed using the log-rank, chi(2) and Mann-Whitney U test. RESULTS: There were 2 (7%) ISR among DES versus 14 (58%) ISR among BMS (P = .0002) patients, with a longer time of freedom from IRS after DES implantation (P = .022). There were three deaths (18%) among DES, four (31%) with BMS, and one (14%) with DES and BMS (P = NS). Left anterior descending artery was the place of DES implantation in 17 (61%) versus 10 (42%) of BMS cases (P = NS). Risk factor profile was comparable except for a higher age at the time of transplantation (46 +/- 7 vs 41 +/- 6 years; P = .011) and stent implantation (54 +/- 7 vs 49 +/- 6 years; P = .0002) for DES. CONCLUSION: Favorable long-term results of sirolimus-eluting stents over BMS implanted for TxCAD suggested their preferential use in heart transplant recipients.

Transplant Proc. 2007 Nov;39(9):2859-61

ENHANCED EXTERNAL COUNTER PULSATION (EECP) AS A NOVEL TREATMENT FOR RESTLESS LEGS SYNDROME (RLS): A PRELIMINARY TEST OF THE VASCULAR NEUROLOGIC HYPOTHESIS FOR RLS.

BACKGROUND AND PURPOSE: Enhanced external counter pulsation (EECP) is used to treat angina. With sustained treatment this increases collateral circulation to the coronary arteries as well as to the body as a whole. We found some patients who underwent EECP for angina or congestive heart failure who also coincidentally had severe Restless Legs Syndrome (RLS). Case reports are presented. PATIENTS AND METHODS: Six patients with RLS (1F, 5M, ages 55-80) underwent EECP treatment. All patients were given the International RLS Study Group rating scale for RLS (the IRLS) before and immediately after 35 days of EECP treatment. RESULTS: The average IRLS rating scale score of the six patients before treatment was 28.8 (range 23-35), which indicates frequent and moderate to very severe RLS. After 35 days of EECP treatment the IRLS score was 6 (P<0.03), which indicates clinically insignificant RLS. Long-term follow-up in three patients indicates sustained improvement in all three at 3-6 months after EECP was completed (IRLS score 28.3-3.33). Further follow-up in four patients showed sustained improvement in two patients 1 year after EECP was completed. CONCLUSION: EECP improves RLS symptoms significantly and could be considered as an adjunct treatment for patients with RLS. In some cases, the improvement lasts for months after the course of treatment. In this way EECP is unique and unlike pharmacotherapy which requires continuous daily treatment. Furthermore, our results suggest that decreases in vascular flow influence the peripheral or central nervous system leading to the sensory symptoms of RLS. A larger number of patients studied under blinded conditions is needed to draw further conclusions.

Sleep Med. 2005 Mar;6(2):101-6

AN ANALYSIS OF THE EFFICACY AND SAFETY OF ENHANCED EXTERNAL COUNTERPULSATION AT WEST VIRGINIA UNIVERSITY HOSPITALS.

A retrospective analysis was conducted of 79 consecutive patients who underwent enhanced external counterpulsation (EECP) at West Virginia University Hospitals during the period of November 1998 to September 2005 to determine its efficacy and safety in treating angina. A chart review and/or phone survey was performed to analyze pertinent clinical data (sublingual nitroglycerin use and angina class) pre and post EECP. A total of 60 (76%) patients who were referred for EECP successfully finished the 35 treatments. Seventy-five percent of the patient population improved at least one angina class after a full course of treatment. Therapy was discontinued due to adverse effects in 12 (15%) patients. Statistically significant improvements in angina class and reduction in anti-angina medications were observed in every co-morbid subgroup analyzed, including patients with peripheral

vascular disease, diabetes, hyperlipidemia, hypertension, smoking, Post-MI, and LVEF < 40% (P < .05, Wilcoxon Signed-Rank test). Overall, EECP was effective in improving angina as reflected in a substantial reduction in antiangina medications in 59 (75%) patients.

W V Med J. 2007 May-Jun;103(3):10-2

ENHANCED EXTERNAL COUNTERPULSATION AND FUTURE DIRECTIONS: STEP BEYOND MEDICAL MANAGEMENT FOR PATIENTS WITH ANGINA AND HEART FAILURE.

Between 25,000 and 75,000 new cases of angina refractory to maximal medical therapy and standard coronary revascularization procedures are diagnosed each year. In addition, heart failure also places an enormous burden on the U.S. health care system, with an estimated economic impact ranging from \$20 billion to more than \$50 billion per year. The technique of counterpulsation, studied for almost one-half century now, is considered a safe, highly beneficial, low-cost, noninvasive treatment for these angina patients, and now for heart failure patients as well. Recent evidence suggests that enhanced external counterpulsation (EECP) therapy may improve symptoms and decrease long-term morbidity via more than 1 mechanism, including improvement in endothelial function, promotion of collateralization, enhancement of ventricular function, improvement in oxygen consumption (VO₂), regression of atherosclerosis, and peripheral training effects similar to exercise. Numerous clinical trials in the last 2 decades have shown EECP therapy to be safe and effective for patients with refractory angina with a clinical response rate averaging 70% to 80%, which is sustained up to 5 years. It is not only safe in patients with coexisting heart failure, but also is shown to improve quality of life and exercise capacity and to improve left ventricular function long-term. Interestingly, EECP therapy has been studied for various potential uses other than heart disease, such as restless leg syndrome, sudden deafness, hepatorenal syndrome, erectile dysfunction, and so on. This review summarizes the current evidence for its use in stable angina and heart failure and its future directions.

J Am Coll Cardiol. 2007 Oct 16;50(16):1523-31

THE ROLE OF ENHANCED EXTERNAL COUNTERPULSATION IN THE TREATMENT OF ANGINA AND HEART FAILURE.

As the incidence of angina and heart failure continue to rise, new therapeutic options will be needed to treat patients who remain symptomatic or who are intolerant to current treatment. Enhanced external counterpulsation (EECP) is a noninvasive modality being investigated in both angina and congestive heart failure patients. It has been proven to provide symptomatic benefit in angina patients, but has not been proven to show an increase in life expectancy or decrease in cardiovascular events. EECP in heart failure has been proven to be safe, but its efficacy is still uncertain. The present paper summarizes the current literature on the clinical use of EECP in angina and heart failure.

Can J Cardiol. 2007 Aug;23(10):779-81

A NEW TREATMENT MODALITY IN HEART FAILURE ENHANCED EXTERNAL COUNTERPULSATION (EECP).

Heart failure remains a significant health problem in the United States and in the world. Despite a surfeit of recent diagnostic and therapeutic advances, patients with heart failure remain inadequately helped. The overwhelming need for new and better therapies continues to stimulate scientists to investigate new technologies. Over the past several years the use of enhanced external counterpulsation as a treatment for chronic angina has steadily increased. Recently, its potential role in heart failure management has been shown. We review the role of enhanced external counterpulsation in heart failure management as an emerging noninvasive outpatient therapy.

Cardiol Rev. 2004 Jan-Feb;12(1):15-20

EFFECTS OF ENHANCED EXTERNAL COUNTERPULSATION ON ANGINAL SYMPTOMS AND IMPROVEMENTS IN OBJECTIVE MEASURES OF MYOCARDIAL ISCHAEMIA.

BACKGROUND: Enhanced external counterpulsation (EECP) is a novel, potentially beneficial adjunct therapy used for angina pectoris. We assessed the efficacy of this method in relieving angina and improving objective measures of myocardial ischaemia. **METHODS:** All patients (67) who referred for EECP to Shahid Chamran Hospital, Isfahan, Iran from 2002 to 2005 were included. Demographic data, coronary artery disease (CAD) risk factors and baseline angiographic data were collected. Anginal symptoms, Canadian Cardiovascular Society (CCS) functional class, echocardiographic parameters (ejection fraction, left ventricular end-diastolic and end-systolic diameters) and exercise test duration before and after the treatment were compared. **RESULTS:** Seventy-seven per cent of patients who had undergone EECP had a positive clinical response. Exercise test duration and CCS functional class improved after the treatment. However, EECP had no significant effect on echocardiographic parameters. Efficacy was independent of age, gender, CAD risk factors, prior CCS functional class and echocardiographic parameters. Patients without left main artery involvement and those who had at least one non-obstructed artery demonstrated a

greater likelihood of improvement. **CONCLUSION:** The results of this study suggested that EECP is a safe, well tolerated, and significantly effective treatment for angina pectoris.

Cardiovasc J Afr. 2007 May-Jun;18(3):154-6

TWO-YEAR CLINICAL OUTCOMES AFTER ENHANCED EXTERNAL COUNTERPULSATION (EECP) THERAPY IN PATIENTS WITH REFRACTORY ANGINA PECTORIS AND LEFT VENTRICULAR DYSFUNCTION (REPORT FROM THE INTERNATIONAL EECP PATIENT REGISTRY).

Enhanced external counterpulsation (EECP) is a noninvasive circulatory assist device that has recently emerged as a treatment option for refractory angina in left ventricular (LV) dysfunction. This 2-year cohort study describes the long-term follow-up of patients who had severe LV dysfunction that was treated with EECP for angina pectoris and reports clinical outcomes, event-free survival rates, and the incidence of repeat EECP. This study included 363 patients who had refractory angina and LV ejection fraction $\leq 35\%$. Most patients reported quality of life as poor. After completion of treatment, there was a significant decrease in severity of angina class ($p < 0.001$), and 72% improved from severe angina to no angina or mild angina. Fifty-two percent of patients discontinued nitroglycerin use. Quality of life improved substantially. At 2 years this decrease in angina was maintained in 55% of patients. The 2-year survival rate was 83%, and the major adverse cardiovascular event-free survival rate was 70%. Forty-three percent had no reported cardiac hospitalization; 81% had no reported congestive heart failure events. Repeat EECP was performed in 20% of these patients. The only significant independent predictor of repeat EECP in a proportional hazard model was failure to complete the first EECP treatment course (hazard ratio 2.9, 95% confidence interval 1.7 to 4.9). Improvements in angina symptoms and quality of life were maintained at 2 years. In conclusion, for patients who have high-risk LV dysfunction, EECP offers an effective, durable therapeutic approach for refractory angina. Decreased angina and improvement in quality of life were maintained at 2 years, with modest repeat EECP and low major cardiovascular event rates.

Am J Cardiol. 2006 Jan 1;97(1):17-20

ONE YEAR FOLLOW-UP OF PATIENTS WITH REFRACTORY ANGINA PECTORIS TREATED WITH ENHANCED EXTERNAL COUNTERPULSATION.

BACKGROUND: Enhanced external counterpulsation (EECP) is a non-invasive technique that has been shown to be effective in reducing both angina and myocardial ischemia in patients not responding to medical therapy and without revascularization alternatives. The aim of the present study was to assess the long-term outcome of EECP treatment at a Scandinavian centre, in relieving angina in patients with chronic refractory angina pectoris. **METHODS:** 55 patients were treated with EECP. Canadian cardiovascular society (CCS) class, antianginal medication and adverse clinical events were collected prior to EECP, at the end of the treatment, and at six and 12 months after EECP treatment. Clinical signs and symptoms were recorded. **RESULTS:** EECP treatment significantly improved the CCS class in 79 +/- 6% of the patients with chronic angina pectoris ($p < 0.001$). The reduction in CCS angina class was seen in patients with CCS class III and IV and persisted 12 months after EECP treatment. There was no significant relief in angina in patients with CCS class II prior to EECP treatment. 73 +/- 7% of the patients with a reduction in CCS class after EECP treatment improved one CCS class, and 22 +/- 7% of the patients improved two CCS classes. The improvement of two CCS classes could progress over a six months period and tended to be more prominent in patients with CCS class IV. In accordance with the reduction in CCS classes there was a significant decrease in the weekly nitroglycerin usage ($p < 0.05$). **CONCLUSION:** The results from the present study show that EECP is a safe treatment for highly symptomatic patients with refractory angina. The beneficial effects were sustained during a 12-months follow-up period.

BMC Cardiovasc Disord. 2006 Jun 15;6:28

IMPACT OF EXTERNAL COUNTERPULSATION TREATMENT ON EMERGENCY DEPARTMENT VISITS AND HOSPITALIZATIONS IN REFRACTORY ANGINA PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION.

Patients with refractory angina and left ventricular (LV) dysfunction exert an enormous burden on health care resources primarily because of the number of recurrent emergency department (ED) visits and hospitalizations. Enhanced external counterpulsation (EECP) therapy has emerged as a treatment option for patients with angina and LV dysfunction and has been shown to improve clinical outcomes and LV function. Improvements in symptoms and laboratory assessments in these patients, however, do not necessarily correlate with a reduction in ED visits and hospitalizations. This is the first study to assess the impact of EECP therapy on ED visits and hospitalization rates at 6-month follow-up. This prospective cohort study included 450 patients with LV dysfunction (ejection fraction $< 40\%$) treated with EECP therapy for refractory angina. Clinical outcomes, number of all-cause ED visits, and hospitalizations within the 6 months before EECP therapy were compared with those at 6-month follow-up. Despite the unfavorable risk profile, refractory angina patients with LV dysfunction achieved a substantial reduction in all-cause ED visits and hospitalization rates at 6-month follow-up. EECP therapy appears to offer an effective adjunctive treatment option for this group of patients.

Congest Heart Fail. 2007 Jan-Feb;13(1):36-40

ENHANCED EXTERNAL COUNTERPULSATION IMPROVES EXERCISE DURATION AND PEAK OXYGEN CONSUMPTION IN OLDER PATIENTS WITH HEART FAILURE: A SUBGROUP ANALYSIS OF THE PEECH TRIAL.

The Prospective Evaluation of Enhanced External Counter-pulsation in Congestive Heart Failure (PEECH) trial demonstrated that enhanced external counterpulsation (EECP) therapy increased exercise duration and improved functional status and quality of life without affecting peak oxygen consumption. The authors present data from a prespecified subgroup of elderly patients (65 years or older) enrolled in the PEECH trial. The 2 co-primary end points were the percentage of subjects with a >60-second increase in exercise duration and the percentage of subjects with a >1.25-mL/kg/min increase in peak volume of oxygen consumption. At 6-month follow-up, the exercise responder rate was significantly higher in EECP patients compared with controls ($P=.008$). Further, in contrast to the overall PEECH study, the EECP group demonstrated a significantly higher responder rate for peak oxygen consumption ($P=.017$). The authors conclude that an older subgroup of PEECH subjects confirms the beneficial effect of EECP in patients with chronic, stable, mild-to-moderate heart failure.

Congest Heart Fail. 2006 Nov-Dec;12(6):307-11

ENHANCED EXTERNAL COUNTERPULSATION IMPROVES EXERCISE TOLERANCE IN PATIENTS WITH CHRONIC HEART FAILURE.

OBJECTIVES: The PEECH (Prospective Evaluation of Enhanced External Counter-pulsation in Congestive Heart Failure) study assessed the benefits of enhanced external counterpulsation (EECP) in the treatment of patients with mild-to-moderate heart failure (HF). **BACKGROUND:** Enhanced external counterpulsation reduced angina symptoms and extended time to exercise-induced ischemia in patients with coronary artery disease, angina, and normal left ventricular function. A small pilot study and registry analysis suggested benefits in patients with HF. **METHODS:** We randomized 187 subjects with mild-to-moderate symptoms of HF to either EECP and protocol-defined pharmacologic therapy (PT) or PT alone. Two co-primary end points were pre-defined: the percentage of subjects with a 60 s or more increase in exercise duration and the percentage of subjects with at least 1.25 ml/min/kg increase in peak volume of oxygen uptake (VO₂) at 6 months. **RESULTS:** By the primary intent-to-treat analysis, 35% of subjects in the EECP group and 25% of control subjects increased exercise time by at least 60 s ($p = 0.016$) at 6 months. However, there was no between-group difference in peak VO₂ changes. New York Heart Association (NYHA) functional class improved in the active treatment group at 1 week ($p < 0.01$), 3 months ($p < 0.02$), and 6 months ($p < 0.01$). The Minnesota Living with Heart Failure score improved significantly 1 week ($p < 0.02$) and 3 months after treatment ($p = 0.01$). **CONCLUSIONS:** In this randomized, single-blinded study, EECP improved exercise tolerance, quality of life, and NYHA functional classification without an accompanying increase in peak VO₂.

J Am Coll Cardiol. 2006 Sep 19;48(6):1198-205

EFFECTS OF ENHANCED EXTERNAL COUNTERPULSATION (EECP) ON MYOCARDIAL PERFUSION.

PURPOSE: To evaluate whether enhanced external counterpulsation (EECP) exerts an effect on myocardial perfusion. **METHODS:** Eleven patients with angina were studied before and after 35 sessions of EECP treatment. Myocardial perfusion was quantified with positron emission tomography and intravenous ¹³N-ammonia at rest and after dipyridamole, by means of a two-compartment mathematical model. **CONCLUSION:** The results suggest that EECP has no effect on myocardial perfusion. However, because of the small number of patients in this study and highly variable clinical responses, additional studies are required to corroborate this finding. The beneficial effects of EECP appear to be mediated by other mechanisms.

Am J Ther. 2007 Nov-Dec;14(6):519-23

AN UPDATE ON ENHANCED EXTERNAL COUNTERPULSATION.

The development of advanced revascularization techniques has resulted in the growth of a subset of patients with coronary artery disease who are nonrevascularizable and are considered to have refractory angina. Enhanced external counterpulsation (EECP) has been developed for the management of these patients with chronic, refractory disease. Evidence has shown that through improvement of vascular endothelial function and recruitment of collateral vessels, EECP provides many clinical benefits. These patients experience sustained decreases in angina, improvement in exercise time, improved myocardial perfusion, and enhanced quality of life. Furthermore, EECP appears to be safe and effective in the treatment of angina in patients with impaired systolic function and has similar potential in patients with congestive heart failure.

Clin Cardiol. 2005 Mar;28(3):115-8

EFFECT OF ENHANCED EXTERNAL COUNTERPULSATION ON INFLAMMATORY CYTOKINES AND ADHESION MOLECULES IN PATIENTS WITH ANGINA PECTORIS AND ANGIOGRAPHIC CORONARY ARTERY DISEASE.

Cardiovascular disease is associated with chronic low-level inflammation, as evidenced by elevated circulating proinflammatory cytokines. Experimental evidence suggests that inflammation can be suppressed under conditions of high shear stress. This study was conducted to examine the effects of enhanced external counterpulsation (EECP), a noninvasive therapy that increases endothelial shear stress, on circulating levels of inflammatory biomarkers and adhesion molecules in patients with angina pectoris. Twenty-one patients were randomly assigned to either 35 1-hour treatments at cuff pressures of 300 mm Hg (EECP; n=12) or 75 mm Hg (sham; n=9). Plasma tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and soluble vascular cell adhesion molecule-1 were measured before and after 35 1-hour sessions of treatment or sham. Patients in the EECP group demonstrated reductions in tumor necrosis factor-alpha (6.9+/-2.7 vs 4.9+/-2.5 pg/ml, p<0.01; -29%) and monocyte chemoattractant protein-1 (254.9+/-55.9 vs 190.4+/-47.6 pg/ml, p<0.01; -19%) after treatment, whereas there was no change in the sham group. Changes in soluble vascular cell adhesion molecule-1 were not observed in either group. In conclusion, 35 sessions of EECP decreased circulating levels of proinflammatory biomarkers in patients with symptomatic coronary artery disease.

Am J Cardiol. 2008 Feb 1;101(3):300-2

Lipoic acid

RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE BLIND STUDY ON THE CLINICAL EFFICACY OF A CREAM CONTAINING 5% ALPHA-LIPOIC ACID RELATED TO PHOTOAGEING OF FACIAL SKIN.

BACKGROUND: alpha-lipoic acid (LA) or the reduced form dihydrolipoate (DHLA) is a potent scavenger with anti-inflammatory properties. Previous uncontrolled studies with topical treatment with 5% LA-containing creams indicate a beneficial effect on photoageing skin. **OBJECTIVE:** The purpose of this study was to investigate whether a cream containing 5% LA showed any advantages concerning a number of the criteria associated with ageing of the facial skin, compared with an identical cream lacking LA. **MATERIAL AND METHODS:** Thirty-three women, mean age 54.4 years, were included in this controlled study. After randomization half the face was treated twice daily for 12 weeks with the LA cream and the other half with the control cream. The following methods of assessment were used: self-evaluation by the test subjects, clinical evaluation, photographic evaluation and laser profilometry. Profilometry was performed before the start of treatment and at the end. **RESULTS:** All four methods of assessment showed a statistically significant improvement on the LA-treated half of the face. Laser profilometry, the most objective method used, showed an average decrease in skin roughness of 50.8% (44.9-54.0) on the LA-treated side, compared with 40.7% (32.4-48.7) on the placebo-treated half of the face $P < 0.001$ (Wilcoxon matched pairs test). **CONCLUSIONS:** It is indicated that 12 weeks of treatment with a cream containing 5% LA improves clinical characteristics related to photoageing of facial skin.

Br J Dermatol. 2003 Oct;149(4):841-9

EXERCISE TRAINING AND THE ANTIOXIDANT ALPHA-LIPOIC ACID IN THE TREATMENT OF INSULIN RESISTANCE AND TYPE 2 DIABETES.

One hallmark of the insulin-resistant state of prediabetes and overt type 2 diabetes is an impaired ability of insulin to activate glucose transport in skeletal muscle, due to defects in IRS-1-dependent signaling. An emerging body of evidence indicates that one potential factor in the multifactorial etiology of skeletal muscle insulin resistance is oxidative stress, an imbalance between the cellular exposure to an oxidant stress and the cellular antioxidant defenses. Exposure of skeletal muscle to an oxidant stress leads to impaired insulin signaling and subsequently to reduced glucose transport activity. Numerous studies have demonstrated that treatment of insulin-resistant animals and type 2 diabetic humans with antioxidants, including alpha-lipoic acid (ALA), is associated with improvements in skeletal muscle glucose transport activity and whole-body glucose tolerance. An additional intervention that is effective in ameliorating the skeletal muscle insulin resistance of prediabetes and type 2 diabetes is endurance exercise training. Recent investigations have demonstrated that the combination of exercise training and antioxidant treatment using ALA in an animal model of obesity-associated insulin resistance provides a unique interactive effect resulting in a greater improvement in insulin action on skeletal muscle glucose transport than either intervention individually. Moreover, this interactive effect of exercise training and ALA is due in part to improvements in IRS-1-dependent insulin signaling. These studies highlight the effectiveness of combining endurance exercise training and antioxidants in beneficially modulating the molecular defects in insulin action observed in insulin-resistant skeletal muscle.

Free Radic Biol Med. 2006 Jan 1;40(1):3-12

ALPHA-LIPOIC ACID IN THE TREATMENT OF DIABETIC PERIPHERAL AND CARDIAC AUTONOMIC NEUROPATHY.

Antioxidant treatment has been shown to prevent nerve dysfunction in experimental diabetes, providing a rationale for a potential therapeutic value in diabetic patients. The effects of the antioxidant alpha-lipoic acid (thioctic acid) were studied in two multicenter, randomized, double-blind placebo-controlled trials. In the Alpha-Lipoic Acid in Diabetic Neuropathy Study, 328 patients with NIDDM and symptomatic peripheral neuropathy were randomly assigned to treatment with intravenous infusion of alpha-lipoic acid using three doses (ALA 1,200 mg; 600 mg; 100 mg) or placebo (PLAC) over 3 weeks. The total symptom score (TSS) (pain, burning, paresthesia, and numbness) in the feet decreased significantly from baseline to day 19 in ALA 1,200 and ALA 600 vs. PLAC. Each of the four individual symptom scores was significantly lower in ALA 600 than in PLAC after 19 days (all $P < 0.05$). The total scale of the Hamburg Pain Adjective List (HPAL) was significantly reduced in ALA 1,200 and ALA 600 compared with PLAC after 19 days (both $P < 0.05$). In the Deutsche Kardiale Autonome Neuropathie Studie, patients with NIDDM and cardiac autonomic neuropathy diagnosed by reduced heart rate variability were randomly assigned to treatment with a daily oral dose of 800 mg alpha-lipoic acid (ALA) ($n = 39$) or placebo ($n = 34$) for 4 months. Two out of four parameters of heart

rate variability at rest were significantly improved in ALA compared with placebo. A trend toward a favorable effect of ALA was noted for the remaining two indexes. In both studies, no significant adverse events were observed. In conclusion, intravenous treatment with alpha-lipoic acid (600 mg/day) over 3 weeks is safe and effective in reducing symptoms of diabetic peripheral neuropathy, and oral treatment with 800 mg/day for 4 months may improve cardiac autonomic dysfunction in NIDDM.

Diabetes. 1997 Sep;46 Suppl 2:S62-6

R-ALPHA-LIPOIC ACID AND ACETYL-L: -CARNITINE COMPLEMENTARILY PROMOTE MITOCHONDRIAL BIOGENESIS IN MURINE 3T3-L1 ADIPOCYTES.

AIMS/HYPOTHESIS: The aim of the study was to address the importance of mitochondrial function in insulin resistance and type 2 diabetes, and also to identify effective agents for ameliorating insulin resistance in type 2 diabetes. We examined the effect of two mitochondrial nutrients, R-alpha-lipoic acid (LA) and acetyl-L: -carnitine (ALC), as well as their combined effect, on mitochondrial biogenesis in 3T3-L1 adipocytes. **METHODS:** Mitochondrial mass and oxygen consumption were determined in 3T3-L1 adipocytes cultured in the presence of LA and/or ALC for 24 h. Mitochondrial DNA and mRNA from peroxisome proliferator-activated receptor gamma and alpha (Pparg and Ppara) and carnitine palmitoyl transferase 1a (Cpt1a), as well as several transcription factors involved in mitochondrial biogenesis, were evaluated by real-time PCR or electrophoretic mobility shift (EMSA) assay. Mitochondrial complexes proteins were measured by western blot and fatty acid oxidation was measured by quantifying CO₂ production from [1-(14)C]palmitate. **RESULTS:** Treatments with the combination of LA and ALC at concentrations of 0.1, 1 and 10 μmol/l for 24 h significantly increased mitochondrial mass, expression of mitochondrial DNA, mitochondrial complexes, oxygen consumption and fatty acid oxidation in 3T3L1 adipocytes. These changes were accompanied by an increase in expression of Pparg, Ppara and Cpt1a mRNA, as well as increased expression of peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 alpha (Ppargc1a), mitochondrial transcription factor A (Tfam) and nuclear respiratory factors 1 and 2 (Nrf1 and Nrf2). However, the treatments with LA or ALC alone at the same concentrations showed little effect on mitochondrial function and biogenesis. **CONCLUSIONS/INTERPRETATION:** We conclude that the combination of LA and ALC may act as PPARG/A dual ligands to complementarily promote mitochondrial synthesis and adipocyte metabolism.

Diabetologia. 2008 Jan;51(1):165-74

MITOCHONDRIAL AGEING AND THE BENEFICIAL ROLE OF ALPHA-LIPOIC ACID.

Oxidative damage has been implicated to be a major causative factor in the decline in physiological functions that occur during the ageing process. Mitochondria are known to be a rich source for the production of free radicals and, consequently, mitochondrial components are susceptible to lipid peroxidation (LPO) that decreases respiratory activity. In the present investigation, we have evaluated mitochondrial LPO, 8-oxo-dG, oxidized glutathione, reduced glutathione, ATP, lipoic acid, TCA cycle enzymes and electron transport chain (ETC) complex activities in the brain of young versus aged rats. In aged rats, the contents of LPO, oxidized glutathione and 8-oxo-dG were high whereas reduced glutathione, ATP, lipoic acid, TCA cycle enzymes and ETC complex activities were found to be low. Lipoic acid administration to aged rats reduced the levels of mitochondrial LPO, 8-oxo-dG and oxidized glutathione and enhanced reduced glutathione, ATP, lipoic acid and ETC complex activities. In young rats lipoic acid administration showed only minimal lowering the levels of LPO, 8-oxo-dG and oxidized glutathione and slight increase in the levels of reduced glutathione, ATP, lipoic acid, TCA cycle enzymes and ETC complex activities. These findings suggest that the dithiol, lipoic acid, provides protection against age-related oxidative damage in the mitochondria of aged rats.

Neurochem Res. 2007 Sep;32(9):1552-8

DIETARY ALPHA-LIPOIC ACID SUPPLEMENTATION INHIBITS ATHEROSCLEROTIC LESION DEVELOPMENT IN APOLIPOPROTEIN E-DEFICIENT AND APOLIPOPROTEIN E/LOW-DENSITY LIPOPROTEIN RECEPTOR-DEFICIENT MICE.

BACKGROUND: Vascular inflammation and lipid deposition are prominent features of atherosclerotic lesion formation. We have shown previously that the dithiol compound alpha-lipoic acid (LA) exerts antiinflammatory effects by inhibiting tumor necrosis factor-alpha- and lipopolysaccharide-induced endothelial and monocyte activation in vitro and lipopolysaccharide-induced acute inflammatory responses in vivo. Here, we investigated whether LA inhibits atherosclerosis in apolipoprotein E-deficient (apoE^{-/-}) and apoE/low-density lipoprotein receptor-deficient mice, 2 well-established animal models of human atherosclerosis. **METHODS AND RESULTS:** Four-week-old female apoE^{-/-} mice (n=20 per group) or apoE/low-density lipoprotein receptor-deficient mice (n=21 per group) were fed for 10 weeks a Western-type chow diet containing 15% fat and 0.125% cholesterol without or with 0.2% (wt/wt) R,S-LA or a normal chow diet containing 4% fat without or with 0.2% (wt/wt) R-LA, respectively. Supplementation with LA significantly reduced atherosclerotic lesion formation in the aortic sinus of both mouse models by approximately 20% and in the aortic arch and thoracic aorta of apoE^{-/-} and apoE/low-density lipoprotein receptor-deficient mice by approximately 55% and 40%, respectively. This strong antiatherogenic effect of LA was associated with almost 40% less body weight gain and lower serum and very low-density lipoprotein levels of triglycerides but not cholesterol. In addition, LA supplementation reduced

aortic expression of adhesion molecules and proinflammatory cytokines and aortic macrophage accumulation. These antiinflammatory effects of LA were more pronounced in the aortic arch and the thoracic aorta than in the aortic sinus, reflecting the corresponding reductions in atherosclerosis. **CONCLUSIONS:** Our study shows that dietary LA supplementation inhibits atherosclerotic lesion formation in 2 mouse models of human atherosclerosis, an inhibition that appears to be due to the "antiobesity," antihypertriglyceridemic, and antiinflammatory effects of LA. LA may be a useful adjunct in the prevention and treatment of atherosclerotic vascular diseases.

Circulation. 2008 Jan 22;117(3):421-8

MEMORY IMPAIRMENT, OXIDATIVE DAMAGE AND APOPTOSIS INDUCED BY SPACE RADIATION: AMELIORATIVE POTENTIAL OF ALPHA-LIPOIC ACID.

Exposure to high-energy particle radiation (HZE) may cause oxidative stress and cognitive impairment in the same manner that seen in aged mice. This phenomenon has raised the concerns about the safety of an extended manned mission into deep space where a significant portion of the radiation burden would come from HZE particle radiation. The present study aimed at investigating the role of alpha-lipoic acid against space radiation-induced oxidative stress and antioxidant status in cerebellum and its correlation with cognitive dysfunction. We observed spontaneous motor activities and spatial memory task of mice using pyroelectric infrared sensor and programmed video tracking system, respectively. Whole body irradiation of mice with high-LET (56)Fe beams (500 MeV/nucleon, 1.5 Gy) substantially impaired the reference memory at 30 day post-irradiation; however, no significant effect was observed on motor activities of mice. Acute intraperitoneal treatment of mice with alpha-lipoic acid prior to irradiation significantly attenuated such memory dysfunction. Radiation-induced apoptotic damage in cerebellum was examined using a neuronal-specific terminal deoxynucleotidyl transferase-mediated nick end-labeling method (NeuroTACS). Radiation-induced apoptotic and necrotic cell death of granule cells and Purkinje cells were inhibited significantly by alpha-lipoic acid pretreatment. Alpha-lipoic acid pretreatment exerted a very high magnitude of protection against radiation-induced augmentation of DNA damage (comet tail movement and serum 8-OHdG), lipid peroxidation products (MDA+HAE) and protein carbonyls in mice cerebellum. Further, radiation-induced decline of non-protein sulfhydryl (NP-SH) contents of cerebellum and plasma ferric reducing power (FRAP) was also inhibited by alpha-lipoic acid pre-treatment. Results clearly indicate that alpha-lipoic acid is a potent neuroprotective antioxidant. Moreover, present finding also support the idea suggesting the cerebellar involvement in cognition.

Behav Brain Res. 2008 Mar 5;187(2):387-95

THE LONG-TERM SURVIVAL OF A PATIENT WITH PANCREATIC CANCER WITH METASTASES TO THE LIVER AFTER TREATMENT WITH THE INTRAVENOUS ALPHA-LIPOIC ACID/LOW-DOSE NALTREXONE PROTOCOL.

The authors describe the long-term survival of a patient with pancreatic cancer without any toxic adverse effects. The treatment regimen includes the intravenous alpha-lipoic acid and low-dose naltrexone (ALA-N) protocol and a healthy lifestyle program. The patient was told by a reputable university oncology center in October 2002 that there was little hope for his survival. Today, January 2006, however, he is back at work, free from symptoms, and without appreciable progression of his malignancy. The integrative protocol described in this article may have the possibility of extending the life of a patient who would be customarily considered to be terminal. The authors believe that life scientists will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological platform. But until such protocols come to market, the ALA-N protocol should be studied and considered, given its lack of toxicity at levels reported. Several other patients are on this treatment protocol and appear to be doing well at this time.

Integr Cancer Ther. 2006 Mar;5(1):83-9

ALPHA-LIPOIC ACID MODULATES OVARIAN SURFACE EPITHELIAL CELL GROWTH.

OBJECTIVE: The intracellular redox state plays an important role in controlling inflammation. Clinical and laboratory data suggest that inflammation can lead to tumor progression. We hypothesized that restoring intracellular redox control would inhibit inflammation and subsequently tumor progression. Our studies were designed to investigate the effect of alpha-lipoic acid (ALA), a naturally occurring antioxidant, on a key inflammatory signaling pathway and cell proliferation in normal and tumorigenic ovarian surface epithelial cells. **METHODS:** Normal and tumorigenic ovarian surface epithelial cells were isolated as described by Roby and coworkers [Roby KF, Taylor CC, Sweetwood JP, Cheng Y, Pace JL, Tawpik O, Persons DL, Smith PG, Terranova PF, Development of a syngeneic mouse model for events related to ovarian cancer. *Carcinogen* 2000;21 (4):585. [1]]. The effect of ALA on cellular function was measured in cell proliferation and apoptosis assays. p27(kip1) protein levels were measured by Western analysis. Activation of NF-kappaB dependent transcription was assessed in cell cultures transiently transfected with NF-kappaB controlled reporter constructs. **RESULTS:** Our results reveal that ALA selectively inhibits the growth of tumorigenic as compared to non-tumorigenic ovarian surface epithelial cells. The growth inhibitory effect of ALA is not due to induction of apoptosis but instead is associated with an increase in the half-life of the cyclin-dependent kinase inhibitor, p27(kip1). In parallel to the growth inhibitory effect, ALA also affects a key inflammatory signaling pathway by inhibiting TNFalpha-induced NF-kappaB

signaling activity. CONCLUSIONS: Our studies are the first to show that ALA treatment has a growth inhibitory effect on malignant surface epithelial cells of ovarian origin. We have also confirmed the reproducibility of the immunocompetent mouse ovarian cancer model originally described by Roby and coworkers [Roby KF, Taylor CC, Sweetwood JP, Cheng Y, Pace JL, Tawpik O, Persons DL, Smith PG, Terranova PF, Development of a syngeneic mouse model for events related to ovarian cancer.

Gynecol Oncol. 2006 Oct;103(1):45-52

Zeaxanthin

RISK FACTORS FOR AGE-RELATED MACULOPATHY ARE ASSOCIATED WITH A RELATIVE LACK OF MACULAR PIGMENT.

Macular pigment (MP) is composed of the two dietary carotenoids lutein (L) and zeaxanthin (Z), and is believed to protect against age-related maculopathy (ARM). This study was undertaken to investigate MP optical density with respect to risk factors for ARM, in 828 healthy subjects from an Irish population. MP optical density was measured psychophysically using heterochromatic flicker photometry, serum L and Z were quantified by HPLC, and dietary intake of L and Z was assessed using a validated food-frequency questionnaire. Clinical and personal details were also recorded, with particular attention directed towards risk factors for ARM. We report a statistically significant age-related decline in MP optical density ($r^2=0.082$, $p<0.01$). Current and past smokers had lower average MP optical density than never smokers and this difference was statistically significant ($p<0.01$). Subjects with a confirmed family history of ARM had significantly lower levels of MP optical density than subjects with no known family history of disease ($p<0.01$). For each of these established risk factors, their statistically significant negative association with MP persisted after controlling for the other two, and also after controlling for other potentially confounding variables such as sex, cholesterol, dietary and serum L ($p<0.01$). In the absence of retinal pathology, and in advance of disease onset, the relative lack of MP seen in association with increasing age, tobacco use and family history of ARM supports the hypothesis that the enhanced risk that these variables represent for ARM may be attributable, at least in part, to a parallel deficiency of macular carotenoids.

Exp Eye Res. 2007 Jan;84(1):61-74

PLASMA LUTEIN AND ZEAXANTHIN AND OTHER CAROTENOIDS AS MODIFIABLE RISK FACTORS FOR AGE-RELATED MACULOPATHY AND CATARACT: THE POLA STUDY.

PURPOSE: To assess the associations of plasma lutein and zeaxanthin and other carotenoids with the risk of age-related maculopathy (ARM) and cataract in the population-based Pathologies Oculaires Liées à l'Age (POLA) Study. **METHODS:** Retinal photographs were graded according to the international classification. ARM was defined by the presence of late ARM (neovascular ARM, geographic atrophy) and/or soft indistinct drusen (>125 microm) and/or soft distinct drusen (>125 microm) associated with pigmentary abnormalities. Cataract classification was based on a direct standardized lens examination at the slit lamp, according to Lens Opacities Classification System III. Plasma carotenoids were measured by high-performance liquid chromatography (HPLC), in 899 subjects of the cohort. **RESULTS:** After multivariate adjustment, the highest quintile of plasma zeaxanthin was significantly associated with reduced risk of ARM (OR=0.07; 95% CI: 0.01-0.58; P for trend=0.005), nuclear cataract (OR=0.23; 95% CI: 0.08-0.68; P for trend=0.003) and any cataract (OR=0.53; 95% CI: 0.31-0.89; P for trend=0.01). ARM was significantly associated with combined plasma lutein and zeaxanthin (OR=0.21; 95% CI: 0.05-0.79; P for trend=0.01), and tended to be associated with plasma lutein (OR=0.31; 95% CI: 0.09-1.07; P for trend=0.04), whereas cataract showed no such associations. Among other carotenoids, only beta-carotene showed a significant negative association with nuclear cataract, but not ARM. **CONCLUSIONS:** These results are strongly suggestive of a protective role of the xanthophylls, in particular zeaxanthin, for the protection against ARM and cataract.

Invest Ophthalmol Vis Sci. 2006 Jun;47(6):2329-35

PLASMA CAROTENOIDS AND PROSTATE CANCER: A POPULATION-BASED CASE-CONTROL STUDY IN ARKANSAS.

Carotenoids possess antioxidant properties and thus may protect against prostate cancer. Epidemiological studies of dietary carotenoids and this malignancy were inconsistent, partially due to dietary assessment error. In this study, we aimed to investigate the relation between plasma concentrations of carotenoids and the risk of prostate cancer in a population-based case-control study in Arkansas. Cases ($n = 193$) were men with prostate cancer diagnosed in 3 major hospitals, and controls ($n = 197$) were matched to cases by age, race, and county of residence. After adjustment for confounders, plasma levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin were inversely associated with prostate cancer risk. Subjects in the highest quartile of plasma lycopene (513.7 microg/l) had a 55% lower risk of prostate cancer than those in the lowest quartile (140.5 microg/l; P trend = 0.042). No apparent association was observed for plasma alpha-carotene and beta-carotene. Further adjustment for the other 4 carotenoids did not materially alter the risk estimates for plasma lycopene, lutein/zeaxanthin, and beta-cryptoxanthin but appeared to result in an elevated risk with high levels of plasma alpha-carotene and beta-carotene. The results of all analyses did

not vary substantially by age, race, and smoking status. This study added to the emerging evidence that high circulating levels of lycopene, lutein/zeaxanthin, and beta-cryptoxanthin are associated with a low risk of prostate cancer.

Nutr Cancer. 2007;59(1):46-53

LOW PLASMA LEVELS OF OXYGENATED CAROTENOIDS IN PATIENTS WITH CORONARY ARTERY DISEASE.

BACKGROUND AND AIMS: Low circulating levels of carotenoids have been associated with cardiovascular disease. The distribution of different carotenoids in blood may have an impact on the cardioprotective capacity. The aim of the present study was to determine the plasma levels of 6 major carotenoids in patients with coronary artery disease (CAD) and relate the findings to clinical, metabolic and immune parameters. **METHODS AND RESULTS:** Plasma levels of oxygenated carotenoids (lutein, zeaxanthin, beta-cryptoxanthin) and hydrocarbon carotenoids (alpha-carotene, beta-carotene, lycopene) were determined in 39 patients with acute coronary syndrome, 50 patients with stable CAD and 50 controls. Serological assays for inflammatory activity and flow cytometrical analysis of lymphocyte subsets were performed. Both patient groups had significantly lower plasma levels of oxygenated carotenoids, in particular lutein+zeaxanthin, compared to controls. Low levels of oxygenated carotenoids were associated with smoking, high body mass index (BMI), low high density lipoprotein (HDL) cholesterol and, to a minor degree, inflammatory activity. Plasma levels of lutein+zeaxanthin were independently associated with the proportions of natural killer (NK) cells, but not with other lymphocytes, in blood. **CONCLUSION:** Among carotenoids, lutein+zeaxanthin and beta-cryptoxanthin were significantly reduced in CAD patients independent of clinical setting. The levels were correlated to a number of established cardiovascular risk factors. In addition, the relationship between NK cells and lutein+zeaxanthin may indicate a particular role for certain carotenoids in the immunological scenario of CAD.

Nutr Metab Cardiovasc Dis. 2007 Jul;17(6):448-56

PLASMA CAROTENOID LEVELS AND COGNITIVE PERFORMANCE IN AN ELDERLY POPULATION: RESULTS OF THE EVA STUDY.

BACKGROUND: The hypothesis of carotenoids having a preventive role in cognitive impairment is suggested by their antioxidant properties. **METHODS:** We examined, in a cross-sectional analysis, the relationship between cognitive performance (assessed by the Mini-Mental State Examination, Trail Making Test Part B, Digit Symbol Substitution, Finger Tapping Test, and Word Fluency Test) and different plasma carotenoids (lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, and trans-beta-carotene and cis-beta-carotene) in a healthy elderly population (the EVA, "Etude du Vieillissement Artériel," study; n = 589, age = 73.5 +/- 3 years). **RESULTS:** Logistic regression showed that participants with the lowest cognitive functioning (<25th percentile) had a higher probability of having low levels of specific plasma carotenoids (<1st quartile): lycopene and zeaxanthin. For zeaxanthin, odds ratios (ORs) were as follows: OR(DSS) = 1.97 (95% confidence interval [CI] = 1.21-3.20), OR(FTT) = 1.70 (CI = 1.05-2.74), and OR(WFT) = 1.82 (CI = 1.08-3.07); for lycopene, OR(DSS) = 1.93 (CI = 1.20-3.12) and OR(TMTB) = 1.64 (CI = 1.04-2.59). **CONCLUSION:** Even if it is not possible to affirm if these low levels of carotenoids precede or are the consequence of cognitive impairment, our results suggest that low carotenoid levels could play a role in cognitive impairment. The biological significance of our findings needs further research.

J Gerontol A Biol Sci Med Sci. 2007 Mar;62(3):308-16

IMMUNOPATHOLOGICAL ASPECTS OF AGE-RELATED MACULAR DEGENERATION.

Age-related macular degeneration (AMD) represents a leading cause of blindness worldwide. While the clinical and histopathological aspects of AMD are well characterized, its etiology and pathogenesis remain unclear. Recent findings suggest a role for immunologic processes in AMD pathogenesis, including the age-related generation of extracellular deposits inside the Bruch membrane and beneath the retinal pigment epithelium, recruitment of macrophages for clearance of these deposits, complement activation, recruitment of tissue-destructive macrophages, microglial activation and accumulation, and proinflammatory effects of chronic inflammation by Chlamydia pneumoniae. This review discusses the evidence for the role of inflammation in human AMD and in animal models of AMD.

Semin Immunopathol. 2008 Feb 26

MACULAR PIGMENT: A REVIEW OF CURRENT KNOWLEDGE.

The existence of the macula lutea of the human retina has been known for more than 200 years. It is established that the xanthophylls lutein and zeaxanthin are responsible for the yellow color. The effect of macular photopigments on blue-light filtration and color perception is well established. It has been postulated that the pigment might serve to reduce chromatic aberration and to improve visual acuity. The antioxidant capabilities of these xanthophylls combined with their ability to trap short-wavelength light may serve to protect the outer retina, retinal pigment epithelium, and choriocapillaris from oxidative damage. Current ideas on the pathophysiology of age-related macular degeneration may be compatible with the proposed function of lutein and

zeaxanthin. This review will summarize our knowledge about macular pigment regarding current efforts in research and the epidemiology of age-related eye disease.

Arch Ophthalmol. 2006 Jul;124(7):1038-45

ASSOCIATION BETWEEN VISUAL ACUITY AND MEDICAL AND NON-MEDICAL COSTS IN PATIENTS WITH WET AGE-RELATED MACULAR DEGENERATION IN FRANCE, GERMANY AND ITALY.

INTRODUCTION: Exudative ('wet') age-related macular degeneration (ARMD) is the major cause of blindness in Western developed countries. Treatments aimed at preserving vision are already available and new compounds are under development. Micro-economics information will be pivotal to justifying forthcoming investment. **OBJECTIVE:** This study sought to investigate the costs of exudative ARMD in patients who were actively treated at ophthalmology referral centres in three European countries: France, Germany and Italy. **METHOD:** This cross-sectional observational study was conducted in France, Germany and Italy in 2004. The following data were collected: ARMD description, visual acuity (VA), and the medical and non-medical resources used for ARMD in the preceding year. The economic perspective was that of society. ANOVA for cost variables estimated the impact of ARMD per eye, adjusted for sex and age. Both hospital and ambulatory eye centres were included. Patients with exudative ARMD were stratified into four levels of severity using VA thresholds of 20/200 for the worst eye (WE) and 20/40 for the best eye (BE). The main outcome measure was medical and non-medical costs. **RESULTS:** 360 patients were included (females 60%; mean age 77 years; mean interval since diagnosis 2.3 years). The two groups with the greatest difference in severity of VA loss consisted of BE \geq 20/40, WE \geq 20/200 (27.2% of patients) and BE $<$ 20/40, WE $<$ 20/200 (25.5% of patients). Total cost was two-thirds medical and one-third non-medical. Total costs increased with ARMD severity and were 1.1-2 times greater for severe disease compared with less severe disease. Average medical costs (2004 values) in France were euro 3714, compared with euro 1810 in Germany and euro 2020 in Italy, and showed slight increases with ARMD severity. Non-medical costs were significantly higher for patients with severe disease and highest in Germany. **CONCLUSION:**

The impact of ARMD on costs was considerable and a positive correlation was found between total costs and ARMD severity. Differences among countries were partly explained by differences in customary care delivery.

Drugs Aging. 2008;25(3):255-68

NUTRITIONAL SUPPLEMENTATION TO PREVENT CATARACT FORMATION.

Age-related cataract (ARC) is the leading cause of blindness in the world, particularly in developing countries. In contrast, cataract surgery has become the most frequent surgical procedure in people aged 65 years or older in the Western world, causing a considerable financial burden to the health care system. The development of cataracts is mainly an age-related phenomenon, although socioeconomic and lifestyle factors appear to influence their development, e.g. smoking has been found to directly influence ARC. A key role in the pathomechanism of the crystalline lens alteration is played by glucose metabolism and associated affected redox potential, which may induce oxidative damages. Aldose reductase blockers were able to prevent the development of diabetic cataracts in experimental studies, however clinical trials were interrupted due to unclear side effects. Other drugs with radical scavenging properties were effective in in vitro and in vivo experiments, but could not be proven to be efficient and safe in preclinical human trials. A number of epidemiological studies showed an increased risk of nuclear or cortical cataract in people with low blood levels of vitamin E. It is also known that the measured levels of ascorbic acid decline with increasing age in the lens. Beta-Carotin and other non-polar carotenoids seem to be missing and may therefore only play a minor role. Polarized carotenoid lutein and zeaxanthin are available in low concentrations and may therefore have some direct effects. The results of the present interventional studies are still controversial. While the Linxian studies indicated that the prevalence for nuclear cataract was reduced by the supplementation with retinol/zinc or vitamin C/molybdenum, the AREDS trial showed no effect of the antioxidant formulation on the development or progression of ARC. Again, while the REACT study demonstrated a statistically significant positive treatment effect 2 years after treatment for the US patients and for both subgroups (US & UK) after 3 years, no effect was observed in UK patients alone. In another US study, the Physician Health Study, no positive or negative effect of Beta-carotin was observed. Taken together, these studies suggest that any effect of antioxidants on cataract development is likely to be very small and probably is of no clinical or public health significance, thus removing a major rationale for 'anticataract' vitamin supplementation among health-conscious individuals.

Dev Ophthalmol. 2005;38:103-19

CATARACT SURGERY AND QUALITY OF LIFE IMPLICATIONS.

Cataract surgery in the developed world has undergone a revolution over the last 20 years. An operation which used to require a stay in hospital and long visual rehabilitation is now a quick day-case procedure with immediate benefits. As with any surgery there is an associated morbidity, but there is now the potential to provide cataract surgery at an earlier stage of cataract maturation and save patients from a period of severe visual impairment. This article reviews the new techniques available to measure the impact that cataracts have not only on a patient's visual acuity but also their general physical health, function,

cognition, and emotional well-being. New research is described that takes into account these more holistic tests and how they can be used to judge the best time to refer and operate on a patient with cataracts.

Clin Interv Aging. 2007;2(1):105-8

INTAKE OF VITAMIN A AND CAROTENOIDS FROM THE ITALIAN POPULATION—RESULTS OF AN ITALIAN TOTAL DIET STUDY.

The present study focused on vitamin A and carotenoids (alpha- and beta-carotene, lutein and zeaxanthin, beta-cryptoxanthin, lycopene) daily intake from the Italian total diet. The input of some food groups (cereals, vegetables, fruits, milk and dairy, meat and meat products, fish) most responsible for major and minor contributions to the daily intake of these molecules was evaluated. Furthermore the contribution to the dietary intake of beta-carotene and lutein of the most consumed vegetables in the market basket of the Italian total diet (beets, brassica vegetables, carrots, chicory, courgette (zucchini), green beans, lettuce, peas, pepper, spinach, tomatoes) was also investigated. Vitamin A daily intake was 855 mg/person/day. The vegetables food group made the greatest contribution (37%), followed by the meat and meat products food group (23%). The Italian total diet provided 14.3 mg/person/day of carotenoids; lycopene was the highest (7.4 mg/day), followed by lutein + zeaxanthin (4 mg/day), beta-carotene (2.6 mg/day), alpha-carotene (0.15 mg/day), and beta-cryptoxanthin (0.17 mg/day). Carrots and tomatoes were the main sources of beta-carotene in the diet, otherwise the daily consumption of leafy vegetables (spinach, beets, lettuce) made the main contribution to lutein + zeaxanthin daily intake.

Int J Vitam Nutr Res. 2006 May;76(3):103-9

LUTEIN AND ZEAXANTHIN AND THEIR POTENTIAL ROLES IN DISEASE PREVENTION.

Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. They are widely distributed in tissues and are the principal carotenoids in the eye lens and macular region of the retina. Epidemiologic studies indicating an inverse relationship between xanthophyll intake or status and both cataract and age-related macular degeneration suggest these compounds can play a protective role in the eye. Some observational studies have also shown these xanthophylls may help reduce the risk of certain types of cancer, particularly those of the breast and lung. Emerging studies suggest as well a potential contribution of lutein and zeaxanthin to the prevention of heart disease and stroke. Even as the evidence for a role of lutein and zeaxanthin in disease prevention continues to evolve, particularly from human studies directed to their bioavailability, metabolism, and dose-response relationships with intermediary biomarkers and clinical outcomes, it is worth noting that recommendations to consume foods rich in xanthophylls are consistent with current dietary guidelines.

J Am Coll Nutr. 2004 Dec;23(6 Suppl):567S-587S

APPLICATION OF NUTRIGENOMICS IN EYE HEALTH.

This paper reviews recent findings on the implication of nutritional and genetic factors in age-related eye diseases: age-related macular degeneration (AMD; a degenerative disease of the retina) and cataract (opacification of the lens). Because of direct exposure to light, the eye is particularly sensitive to oxidative stress. Antioxidants, such as vitamin E, C or zinc, clearly have a protective effect in AMD and probably in cataract. In addition, two carotenoids, lutein and zeaxanthin, may play a more specific role in the eye: they accumulate in the retina, where they form the macular pigment, and in the lens. Their role is probably to filter out phototoxic blue light and to quench singlet oxygen. Finally, docosahexaenoic acid (an omega-3 polyunsaturated fatty acid) is particularly important for the retina, where it exerts structural, functional and protective actions. Besides, these diseases are strongly influenced by genetics, as demonstrated by familial and twin studies. The apolipoprotein E4 allele is associated with a reduced risk of AMD, while an association of AMD with complement factor H polymorphism has recently been demonstrated. Nutrigenomics, by studying the interactions between genetic variability and nutritional factors, represents a new challenge in order to account for interindividual variations in disease susceptibility. Such potential interactions are presented.

Forum Nutr. 2007;60:168-75

LUTEIN AND ZEAXANTHIN DIETARY SUPPLEMENTS RAISE MACULAR PIGMENT DENSITY AND SERUM CONCENTRATIONS OF THESE CAROTENOIDS IN HUMANS.

Age-related macular degeneration (AMD) is thought to be the result of a lifetime of oxidative insult that results in photoreceptor death within the macula. Increased risk of AMD may result from low levels of lutein and zeaxanthin (macular pigment) in the diet, serum or retina, and excessive exposure to blue light. Through its light-screening capacity and antioxidant activity, macular pigment may reduce photooxidation in the central retina. Lutein supplements, at 30 mg/d, were shown previously to increase serum lutein and macular pigment density in two subjects. In this study, we compared the effects of a range of lutein doses (2.4-30 mg/d), as well as a high zeaxanthin dose (30 mg/d), on the serum and macular pigment in a series of experiments. Serum carotenoids were quantified by HPLC. Macular pigment densities were determined psychophysically. Serum lutein

concentrations in each subject reached a plateau that was correlated with the dose ($r = 0.82$, $P < 0.001$). Plateau concentrations ranged from 2.8×10^{-7} to 2.7×10^{-6} mol/L. Zeaxanthin was less well absorbed than an equal lutein dose, resulting in plateaus of approximately 5×10^{-7} mol/L. The rate of increase in macular pigment optical density was correlated with the plateau concentration of carotenoids in the serum ($r = 0.58$, $P < 0.001$), but not with the presupplementation optical density ($r = 0.13$, $P = 0.21$). The mean rate of increase was $(3.42 \pm 0.80) \times 10^5$ mAU/d per unit concentration (mol/L) of carotenoids in the serum. It remains to be demonstrated whether lutein or zeaxanthin dietary supplements reduce the incidence of AMD.

J Nutr. 2003 Apr;133(4):992-8

LYCOPENE AND BETA-CAROTENE DECOMPOSE MORE RAPIDLY THAN LUTEIN AND ZEAXANTHIN UPON EXPOSURE TO VARIOUS PRO-OXIDANTS IN VITRO.

Major carotenoids of human plasma and tissues were exposed to radical-initiated autoxidation conditions. The consumption of lutein and zeaxanthin, the only carotenoids in the retina, and lycopene and beta-carotene, the most effective quenchers of singlet oxygen in plasma, were compared. Under all conditions of free radical-initiated autoxidation of carotenoids which were investigated, the breakdown of lycopene and beta-carotene was much faster than that of lutein and zeaxanthin. Under the influence of UV light in presence of Rose Bengal, by far the highest breakdown rate was found for beta-carotene, followed by lycopene. Bleaching of carotenoid mixtures mediated by NaOCl, addition of azo-bis-isobutyronitril (AIBN), and the photoirradiation of carotenoid mixtures by natural sunlight lead to the following sequence of breakdown rates: lycopene > beta-carotene > zeaxanthin > lutein. The slow degradation of the xanthophylls zeaxanthin and lutein may be suggested to explain the majority of zeaxanthin and lutein in the retina of man and other species. In correspondence to that, the rapid degradation of beta-carotene and lycopene under the influence of natural sunlight and UV light is postulated to be the reason for the almost lack of those two carotenoids in the human retina. Nevertheless, a final proof of that theory is lacking.

Biofactors. 1999;10(2-3):105-13

THE RETINAL CAROTENOIDS ZEAXANTHIN AND LUTEIN SCAVENGE SUPEROXIDE AND HYDROXYL RADICALS: A CHEMILUMINESCENCE AND ESR STUDY.

PURPOSE: Carotenoids are present in many biological systems, often decreasing the formation of products of oxidative damage to biological molecules. In the macula their concentration is so high that it has been believed that the yellow color filters out damaging blue light. Recent reports that dietary lutein reduces the risk of cataract in the eye lens suggested that the antioxidant action of carotenoids, which has been inferred from decreased oxidative damage, warranted further direct investigation.

METHODS: Superoxide and hydroxyl radical scavenging by lutein and zeaxanthin (retinal carotenoids), beta-carotene, lycopene, lutein esters (from marigolds), and a commercial mixture of soy carotenoids were compared to scavenging by ascorbate and ascorbyl palmitate. Radical scavenging was measured with a chemiluminescent assay (luminol) and by electron spin resonance, ESR. Inhibitory concentrations, IC(50), were determined with the luminescent assay. **RESULTS:** All of the carotenoids scavenged both superoxide (in ESR 30-50% at 16.7 microM) and hydroxyl radicals (in ESR 50-70% at 16.7 microM, in a luminescent assay 90-99%). **CONCLUSIONS:** While crocin may be unable to scavenge superoxide, some of the other carotenoids do so quite effectively. The mixtures of 15,15'-cis and all-trans-carotenoids studied by ESR and luminescent assay scavenge both superoxide and hydroxyl radicals. Lycopene and beta-carotene both scavenge superoxide more effectively than the xanthophylls of the retina, zeaxanthin and lutein. All of the carotenoids examined scavenged the hydroxyl radicals more effectively than superoxide radicals. The predominant carotenoid in the fovea of the retina, zeaxanthin, scavenged hydroxyl radicals more effectively than the other retinal carotenoid, lutein. Possible mechanisms of radical scavenging by the carotenoids are discussed.

Mol Vis. 2006 Sep 30;12:1127-35

THE MACULAR XANTHOPHYLLS.

The macular pigments are predominantly composed of three carotenoids: lutein, zeaxanthin, and meso-zeaxanthin. These carotenoids are concentrated and distributed in a selective manner. The properties of these pigments are further explored along with their methods of uptake, stabilization, and storage. The dual nature of these pigments as filters and antioxidants are elaborated upon in relation to their protective effects upon the macula, specifically in age-related macular degeneration. Evidence suggests that increased levels of macular pigment are correlated with a decreased risk of age-related macular degeneration. Many have sought to exploit this therapeutic relation. Studies reveal that oral supplementation with lutein and zeaxanthin can increase the levels of macular pigments in the retina and plasma. The effects of such supplementation on actual ocular function have yet to be fully addressed. New and standardized methods of assessing macular pigment density are discussed and future areas of research to further our understanding of macular xanthophylls as they pertain to age-related macular degeneration are highlighted.

Surv Ophthalmol. 2005 Mar-Apr;50(2):183-93

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