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Journal ABSTRACTS

CoQ10

THE EMERGING ROLE OF COENZYME Q-10 IN AGING, NEURODEGENERATION, CARDIOVASCULAR DISEASE, CANCER AND DIABETES MELLITUS.

Coenzyme Q (ubiquinone, 2-methyl-5,6-dimethoxy-1,4-benzoquinone), soluble natural fat quinone, is crucial to optimal biological function. The coenzyme Q molecule has amphipathic (biphasic) properties due to the hydrophilic benzoquinone ring and the lipophilic poly isoprenoid side-chain. The nomenclature of coenzyme Q-n is based on the amount of isoprenoid units attached to 6-position on the benzoquinone ring. It was demonstrated that coenzyme Q, in addition to its role in electron transport and proton transfer in mitochondrial and bacterial respiration, acts in its reduced form (ubiquinol) as an antioxidant. Coenzyme Q-10 functions as a lipid antioxidant regulating membrane fluidity, recycling radical forms of vitamin C and E, and protecting membrane phospholipids against peroxidation. The antioxidant property, high degree of hydrophobicity and universal occurrence in biological system, suggest an important role for ubiquinone and ubiquinol in cellular defense against oxidative damage. Coenzyme Q-10 is a ubiquitous and endogenous lipid-soluble antioxidant found in all organisms. Neurodegenerative disorders, cancer, cardiovascular diseases and diabetes mellitus and especially aging and Alzheimer's disease exhibit altered levels of ubiquinone or ubiquinol, indicating their likely crucial role in the pathogenesis and cellular mechanisms of these ailments. This review is geared to discuss the biological effect of coenzyme Q with an emphasis on its impact in initiation, progression, treatment and prevention of neurodegenerative, cardiovascular and carcinogenic diseases.

Curr Neurovasc Res. 2005 Dec;2(5):447-59

IMPROVEMENT OF VISUAL FUNCTIONS AND FUNDUS ALTERATIONS IN EARLY AGE-RELATED MACULAR DEGENERATION TREATED WITH A COMBINATION OF ACETYL-L-CARNITINE, N-3 FATTY ACIDS, AND COENZYME Q10.

The aim of this randomized, double-blind, placebo-controlled clinical trial was to determine the efficacy of a combination of acetyl-L-carnitine, n-3 fatty acids, and coenzyme Q10 (Phototrop) on the visual functions and fundus alterations in early age-related macular degeneration (AMD). One hundred and six patients with a clinical diagnosis of early AMD were randomized to the treated or control groups. The primary efficacy variable was the change in the visual field mean defect (VFMD) from baseline to 12 months of treatment, with secondary efficacy parameters: visual acuity (Snellen chart and ETDRS chart), foveal sensitivity as measured by perimetry, and fundus alterations as evaluated according to the criteria of the International Classification and Grading System for AMD. The mean change in all four parameters of visual functions showed significant improvement in the treated group by the end of the study period. In addition, in the treated group only 1 out of 48 cases (2%) while in the placebo group 9 out of 53 (17%) showed clinically significant (>2.0 dB) worsening in VFMD ($p = 0.006$, odds ratio: 10.93). Decrease in drusen-covered area of treated eyes was also statistically significant as compared to placebo when either the most affected eyes ($p = 0.045$) or the less affected eyes ($p = 0.017$) were considered. These findings strongly suggested that an appropriate combination of compounds which affect mitochondrial lipid metabolism, may improve and subsequently stabilize visual functions, and it may also improve fundus alterations in patients affected by early AMD.

Ophthalmologica. 2005 May-Jun;219(3):154-66

LOW PLASMA COENZYME Q10 LEVELS AS AN INDEPENDENT PROGNOSTIC FACTOR FOR MELANOMA PROGRESSION.

BACKGROUND: Abnormally low plasma levels of coenzyme Q10 (CoQ10) have been found in patients with cancer of the breast, lung, or pancreas. **OBJECTIVE:** A prospective study of patients with melanoma was conducted to assess the usefulness of CoQ10 plasma levels in predicting the risk of metastasis and the duration of the metastasis-free interval. **METHODS:** Between January 1997 and August 2004, plasma CoQ10 levels were measured with high-performance liquid chromatography in 117 consecutive melanoma patients without clinical or instrumental evidence of metastasis according to American Joint Committee on Cancer criteria and in 125 matched volunteers without clinically suspect pigmented lesions. Patients taking CoQ10 or cholesterol-lowering medications and those with a diagnosis of diabetes mellitus were excluded from the study. Multiple

statistical methods were used to evaluate differences between patients and control subjects and between patients who did (32.5%) and did not (67.5%) develop metastases during follow-up. RESULTS: CoQ10 levels were significantly lower in patients than in control subjects (t test: $P < .0001$) and in patients who developed metastases than in the metastasis-free subgroup (t test: $P < .0001$). Logistic regression analysis indicated that plasma CoQ10 levels were a significant predictor of metastasis ($P = .0013$). The odds ratio for metastatic disease in patients with CoQ10 levels that were less than 0.6 mg/L (the low-end value of the range measured in a normal population) was 7.9, and the metastasis-free interval was almost double in patients with CoQ10 levels 0.6 mg/L or higher (Kaplan-Meier analysis: $P < .001$). LIMITATIONS: A study with a larger sample, which is currently being recruited, and a longer follow-up will doubtlessly increase the statistical power and enable survival statistics to be obtained. CONCLUSIONS: Analysis of our findings suggests that baseline plasma CoQ10 levels are a powerful and independent prognostic factor that can be used to estimate the risk for melanoma progression.

J Am Acad Dermatol. 2006 Feb;54(2):234-41

AN INCREASE OF OXIDIZED COENZYME Q-10 OCCURS IN THE PLASMA OF SPORADIC ALS PATIENTS.

We have compared plasma redox status of coenzyme Q-10 in 20 sporadic amyotrophic lateral sclerosis (sALS) patients with those in 20 healthy age/sex-matched controls. A significant increase in the oxidized form of coenzyme Q-10 (sALS=109.3+/-95.2 nM; controls=23.3+/-7.5 nM, $P=0.0002$) and in the ratio of oxidized form of coenzyme Q-10 to total coenzyme Q-10 (%CoQ-10) (sALS=12.0+/-9.3%; controls=3.2+/-0.9%, $P<0.0001$) were observed. Moreover, %CoQ-10 correlated significantly with the duration of illness ($\rho=0.494$, $P=0.0315$). Our finding suggests systemic oxidative stress in the pathogenesis of sALS.

J Neurol Sci. 2005 Jan 15;228(1):49-53

TOLERANCE OF HIGH-DOSE (3,000 MG/DAY) COENZYME Q10 IN ALS.

An open-label dose-escalation trial was performed to assess the safety and tolerability of high doses of coenzyme Q10 (CoQ10) in ALS. CoQ10, a cofactor in mitochondrial electron transfer, may improve the mitochondrial dysfunction in ALS. In this study, CoQ10 was safe and well tolerated in 31 subjects treated with doses as high as 3,000 mg/day for 8 months.

Neurology. 2005 Dec 13;65(11):1834-6

MUSCLE BIOPSY IN ALZHEIMER'S DISEASE: MORPHOLOGICAL AND BIOCHEMICAL FINDINGS.

Recent evidences of a predisposing genetic factor associated with Alzheimer's disease (DAT) suggests that important alterations may be expressed in tissues other than the brain. We present morphological and biochemical studies on muscle obtained from ten patients with Alzheimer's disease and coeval controls. Muscle biopsy examination showed an increased subsarcolemmal mitochondrial oxidative activity in three patients. The biochemical studies showed an increased oxidative enzyme activity only in the DAT group. The CoQ10 level, studied so far in three DAT patients, was greatly reduced (approximately 50%) compared with controls. Possible new peripheral markers in Alzheimer's disease will be discussed.

Clin Neuropathol. 1991 Jul-Aug;10(4):171-6.

Benfotiamine

BENFOTIAMINE RELIEVES INFLAMMATORY AND NEUROPATHIC PAIN IN RATS.

Benfotiamine has shown therapeutic efficacy in the treatment of painful diabetic neuropathy in human beings. However, so far there is no evidence about the efficacy of this drug in preclinical models of pain. The purpose of this study was to assess the possible antinociceptive and antialloodynic effect of benfotiamine in inflammatory and neuropathic pain models in the rat. Inflammatory pain was induced by injection of formalin in non-diabetic and diabetic (2 weeks) rats. Reduction of flinching behavior was considered as antinociception. Neuropathic pain was induced by either ligation of left L5/L6 spinal nerves or administration of streptozotocin (50 mg/kg, i.p.) in Wistar rats. Benfotiamine significantly reduced inflammatory (10-300 mg/kg) and neuropathic (75-300 mg/kg) nociception in non-diabetic and diabetic rats. Results indicate that oral administration of benfotiamine is able to reduce tactile allodynia from different origin in the rat and they suggest the use of this drug to reduce inflammatory and neuropathic pain in humans.

Eur J Pharmacol. 2006 Jan 13;530(1-2):48-53

THIAMINE (VITAMIN B(1)) IMPROVES ENDOTHELIUM-DEPENDENT VASODILATATION IN THE PRESENCE OF HYPERGLYCEMIA.

Brachial artery vasoactivity (BAVA) is a reliable, noninvasive method of assessing endothelium-dependent vasodilatation (EDV) in vivo. Acute hyperglycemia, impaired glucose tolerance (IGT), and diabetes mellitus impair EDV, a precursor to atherosclerosis. Thiamine is a coenzyme important in intracellular glucose metabolism. The purpose of this study was to evaluate the effect of thiamine on BAVA in the presence of hyperglycemia. Ten healthy subjects (group H, mean age 27 years), 10 patients with impaired glucose tolerance by World Health Organization criteria (group IGT, mean age 65 years), and 10 patients with non-insulin-dependent diabetes mellitus (group NIDDM, mean age 50 years) were studied. Duplex ultrasound was used to measure brachial artery flow changes in response to reactive hyperemia following brachial artery tourniquet occlusion for 5 min. This test was performed after a 10 hr fast and at 30, 60, and 120 min after a 75 g oral glucose challenge along with measurements of blood glucose level (BGL). A week later, BAVA evaluation was repeated after administration of 100 mg of intravenous thiamine. BAVA (% increased blood flow) at peak and trough BGL was compared with and without thiamine. BAVA at peak glucose improved from 69.0 +/- 6.4% to 152.8 +/- 22.9% in group H ($p < 0.005$), from 57.6 +/- 12.6% to 139.7 +/- 12.4% in group IGT ($p < 0.005$), and from 57.8 +/- 8.3% to 167.8 +/- 11.6% in group NIDDM ($p < 0.005$) following administration of thiamine. On the other hand, at trough glucose levels, BAVA remained essentially unchanged in group H (prethiamine 83.8 +/- 6.5% vs. post-thiamine 83.8 +/- 17.0%, $p > 0.05$) as well as group IGT (prethiamine 96.7 +/- 8.5% vs. post-thiamine 104.0 +/- 17.4%, $p > 0.05$). BAVA at trough glucose was not measured in group NIDDM secondary to trough BGL > 140 mg/dL. EDV was improved by thiamine in the presence of hyperglycemia in healthy subjects and in patients with IGT and NIDDM. The mechanism by which thiamine improves EDV is not due to a glucose-lowering effect as thiamine had no effect on EDV under normoglycemic conditions. Routine administration of thiamine might improve endothelial function and therefore slow the development and progression of atherosclerosis, especially in patients with IGT and NIDDM who are prone to develop accelerated atherosclerosis.

Ann Vasc Surg. 2006 May 31

A REVIEW OF THE BIOCHEMISTRY, METABOLISM AND CLINICAL BENEFITS OF THIAMIN(E) AND ITS DERIVATIVES.

Thiamin(e), also known as vitamin B1, is now known to play a fundamental role in energy metabolism. Its discovery followed from the original early research on the 'anti-beriberi factor' found in rice polishings. After its synthesis in 1936, it led to many years of research to find its action in treating beriberi, a lethal scourge known for thousands of years, particularly in cultures dependent on rice as a staple. This paper refers to the previously described symptomatology of beriberi, emphasizing that it differs from that in pure, experimentally induced thiamine deficiency in human subjects. Emphasis is placed on some of the more unusual manifestations of thiamine deficiency and its potential role in modern nutrition. Its biochemistry and pathophysiology are discussed and some of the less common conditions associated with thiamine deficiency are reviewed. An understanding of the role of thiamine in modern nutrition is crucial in the rapidly advancing knowledge applicable to Complementary Alternative Medicine. References are given that provide insight into the use of this vitamin in clinical conditions that are not usually associated with nutritional deficiency. The role of allithiamine and its synthetic derivatives is discussed. Thiamine plays a vital role in metabolism of glucose. Thus, emphasis is placed on the fact that ingestion of excessive simple carbohydrates

automatically increases the need for this vitamin. This is referred to as high calorie malnutrition.

Evid Based Complement Alternat Med. 2006 Mar;3(1):49-59

THE ROLE OF AGES AND AGE INHIBITORS IN DIABETIC CARDIOVASCULAR DISEASE.

Prolonged hyperglycemia, dyslipidemia and oxidative stress in diabetes result in the production and accumulation of AGEs. It is now clear that AGEs contribute to the development and progression of cardiovascular disease in diabetes, as well as other complications. AGEs are thought to act through receptor-independent and dependent mechanisms to promote vascular damage, fibrosis and inflammation associated with accelerated atherogenesis. As a result, novel therapeutic agents to reduce the accumulation of AGEs in diabetes have gained interest as potential cardioprotective approaches. A variety of agents have been developed which are examined in detail in this review. These include aminoguanidine, ALT-946, pyridoxamine, benfotiamine, OPB-9195, alagebrium chloride, N-phenacylthiazolium bromide and LR-90. In addition, it has been demonstrated that a number of established therapies have the ability to reduce the accumulation of AGEs in diabetes including ACE inhibitors, angiotensin receptor antagonists, metformin, peroxisome proliferators receptor agonists, metal chelators and some antioxidants. The fact that many of these inhibitors of AGEs are effective in experimental models, despite their disparate mechanisms of action, supports the keystone role of AGEs in diabetic vascular damage. Nonetheless, the clinical utility of AGE inhibition remains to be firmly established. Optimal metabolic and blood pressure control, that is achieved early and sustained indefinitely, remains the best recourse for inhibition of AGEs until more specific interventions become a clinical reality.

Curr Drug Targets. 2005 Jun;6(4):453-74

BENFOTIAMINE ACCELERATES THE HEALING OF ISCHAEMIC DIABETIC LIMBS IN MICE THROUGH PROTEIN KINASE B/AKT-MEDIATED POTENTIATION OF ANGIOGENESIS AND INHIBITION OF APOPTOSIS.

AIMS/HYPOTHESIS: Benfotiamine, a vitamin B1 analogue, reportedly prevents diabetic microangiopathy. The aim of this study was to evaluate whether benfotiamine is of benefit in reparative neovascularisation using a type I diabetes model of hindlimb ischaemia. We also investigated the involvement of protein kinase B (PKB)/Akt in the therapeutic effects of benfotiamine. **METHODS:** Streptozotocin-induced diabetic mice, given oral benfotiamine or vehicle, were subjected to unilateral limb ischaemia. Reparative neovascularisation was analysed by histology. The expression of Nos3 and Casp3 was evaluated by real-time PCR, and the activation state of PKB/Akt was assessed by western blot analysis and immunohistochemistry. The functional importance of PKB/Akt in benfotiamine-induced effects was investigated using a dominant-negative construct. **RESULTS:** Diabetic muscles showed reduced transketolase activity, which was corrected by benfotiamine. Importantly, benfotiamine prevented ischaemia-induced toe necrosis, improved hindlimb perfusion and oxygenation, and restored endothelium-dependent vasodilation. Histological studies revealed the improvement of reparative neovascularisation and the inhibition of endothelial and skeletal muscle cell apoptosis. In addition, benfotiamine prevented the vascular accumulation of advanced glycation end products and the induction of pro-apoptotic caspase-3, while restoring proper expression of Nos3 and Akt in ischaemic muscles. The benefits of benfotiamine were nullified by dominant-negative PKB/Akt. In vitro, benfotiamine stimulated the proliferation of human EPCs, while inhibiting apoptosis induced by high glucose. In diabetic mice, the number of circulating EPCs was reduced, with the deficit being corrected by benfotiamine. **CONCLUSIONS/INTERPRETATION:** We have demonstrated, for the first time, that benfotiamine aids the post-ischaemic healing of diabetic animals via PKB/Akt-mediated potentiation of angiogenesis and inhibition of apoptosis. In addition, benfotiamine combats the diabetes-induced deficit in endothelial progenitor cells.

Diabetologia. 2006 Feb;49(2):405-20. Epub 2006 Jan 17

BENFOTIAMINE COUNTERACTS GLUCOSE TOXICITY EFFECTS ON ENDOTHELIAL PROGENITOR CELL DIFFERENTIATION VIA AKT/FOXO SIGNALING.

Dysfunction of mature endothelial cells is thought to play a major role in both micro- and macrovascular complications of diabetes. However, recent advances in biology of endothelial progenitor cells (EPCs) have highlighted their involvement in diabetes complications. To determine the effect of glucotoxicity on EPCs, human EPCs have been isolated from peripheral blood mononuclear cells of healthy donors and cultured in the presence or absence of high glucose (33 mmol/l) or high glucose plus benfotiamine to scavenge glucotoxicity. Morphological analysis revealed that high glucose significantly affected the number of endothelial cell colony forming units, uptake and binding of acLDL and Lectin-1, and the ability to differentiate into CD31- and vascular endothelial growth factor receptor 2-positive cells. Functional analysis outlined a reduced EPC involvement in de novo tube formation, when cocultured with mature endothelial cells (human umbilical vein endothelial cells) on matrigel. To explain the observed phenotypes, we have investigated the signal transduction pathways known to be involved in EPC growth and differentiation. Our results indicate that hyperglycemia impairs EPC differentiation and that the process can be restored by benfotiamine administration, via the modulation of Akt/FoxO1 activity.

Diabetes. 2006 Aug;55(8):2231-7

BENFOTIAMINE PREVENTS MACRO- AND MICROVASCULAR ENDOTHELIAL DYSFUNCTION AND OXIDATIVE STRESS FOLLOWING A MEAL RICH IN ADVANCED GLYCATION END PRODUCTS IN INDIVIDUALS WITH TYPE 2 DIABETES.

OBJECTIVE: Diabetes is characterized by marked postprandial endothelial dysfunction induced by hyperglycemia, hypertriglyceridemia, advanced glycation end products (AGEs), and dicarbonyls (e.g., methylglyoxal [MG]). In vitro hyperglycemia-induced MG formation and endothelial dysfunction could be blocked by benfotiamine, but in vivo effects of benfotiamine on postprandial endothelial dysfunction and MG synthesis have not been investigated in humans until now. **RESEARCH DESIGN AND METHODS:** Thirteen people with type 2 diabetes were given a heat-processed test meal with a high AGE content (HAGE; 15.100 AGE kU, 580 kcal, 54 g protein, 17 g lipids, and 48 g carbohydrates) before and after a 3-day therapy with benfotiamine (1,050 mg/day). Macrovascular flow-mediated dilatation (FMD) and microvascular reactive hyperemia, along with serum markers of endothelial dysfunction (E-selectin, vascular cell adhesion molecule-1, and intracellular adhesion molecule-1), oxidative stress, AGE, and MG were measured during both test meal days after an overnight fast and then at 2, 4, and 6 h postprandially. **RESULTS:** The HAGE induced a maximum reactive hyperemia decrease of -60.0% after 2 h and a maximum FMD impairment of -35.1% after 4 h, without affecting endothelium-independent vasodilatation. The effects of HAGE on both FMD and reactive hyperemia were completely prevented by benfotiamine. Serum markers of endothelial dysfunction and oxidative stress, as well as AGE, increased after HAGE. These effects were significantly reduced by benfotiamine. **CONCLUSIONS:** Our study confirms micro- and macrovascular endothelial dysfunction accompanied by increased oxidative stress following a real-life, heat-processed, AGE-rich meal in individuals with type 2 diabetes and suggests benfotiamine as a potential treatment.

Diabetes Care. 2006 Sep;29(9):2064-71

BENFOTIAMINE IN THE TREATMENT OF DIABETIC POLYNEUROPATHY—A THREE-WEEK RANDOMIZED, CONTROLLED PILOT STUDY (BEDIP STUDY).

OBJECTIVE: The aim of the study was to evaluate the efficacy of benfotiamine administered over three weeks (allithiamine; a lipid-soluble vitamin B1 prodrug with high bioavailability) to patients with diabetic polyneuropathy in a randomized, placebo-controlled, double-blind, two-center pilot study. **MATERIAL AND METHODS:** Forty inpatients (23 male, 18 female, age range 18 - 70 years) with a history of type 1 or 2 diabetes and polyneuropathy of not longer than two years, were included in the study. Twenty Patients received two 50 mg benfotiamine tablets four times daily and 20 patients received placebo over the three-week study period. Two clinical units were involved with 10 patients receiving placebo and 10 patients benfotiamine in each. The neuropathy score according to Katzenwadel et al. [1987] was used to evaluate symptoms of polyneuropathy, vibration perception threshold and both the physician's and the patient's own assessment were documented. **RESULTS:** A statistically significant ($p = 0.0287$) improvement in the neuropathy score was observed in the group given active drug when compared to the placebo-treated controls. There was no statistically significant change observed in the tuning fork test. The most pronounced effect on complaints was a decrease in pain ($p = 0.0414$). More patients in the benfotiamine-treated group than in the placebo group considered their clinical condition to have improved ($p = 0.052$). No side effects attributable to benfotiamine were observed. The differences between the groups cannot be attributed to a change in metabolic parameters since there were no significant alterations in the HbA1 levels and blood sugar profiles. The body mass index of the two groups did not differ. **CONCLUSION:** This pilot investigation (BEDIP Study) has confirmed the results of two earlier randomized controlled trials and has provided further evidence

Int J Clin Pharmacol Ther. 2005 Feb;43(2):71-7

BENFOTIAMINE IS SIMILAR TO THIAMINE IN CORRECTING ENDOTHELIAL CELL DEFECTS INDUCED BY HIGH GLUCOSE.

We investigated the hypothesis that benfotiamine, a lipophilic derivative of thiamine, affects replication delay and generation of advanced glycosylation end-products (AGE) in human umbilical vein endothelial cells cultured in the presence of high glucose. Cells were grown in physiological (5.6 mM) and high (28.0 mM) concentrations of D-glucose, with and without 150 microM thiamine or benfotiamine. Cell proliferation was measured by mitochondrial dehydrogenase activity. AGE generation after 20 days was assessed fluorimetrically. Cell replication was impaired by high glucose (72.3% \pm 5.1% of that in physiological glucose, $p=0.001$). This was corrected by the addition of either thiamine (80.6% \pm 2.4%, $p=0.005$) or benfotiamine (87.5% \pm 8.9%, $p=0.006$), although it not was completely normalized ($p=0.001$ and $p=0.008$, respectively) to that in physiological glucose. Increased AGE production in high glucose (159.7% \pm 38.9% of fluorescence in physiological glucose, $p=0.003$) was reduced by thiamine (113.2% \pm 16.3%, $p=0.008$ vs. high glucose alone) or benfotiamine (135.6% \pm 49.8%, $p=0.03$ vs. high glucose alone) to levels similar to those observed in physiological glucose. Benfotiamine, a derivative of thiamine with better bioavailability, corrects defective replication and increased AGE generation in endothelial cells cultured in high glucose, to a similar extent as thiamine. These effects may result from normalization of accelerated glycolysis and the consequent decrease in metabolites that are extremely active in generating nonenzymatic protein glycation. The potential role of thiamine administration in the prevention or treatment of vascular complications of diabetes deserves further investigation.

VASCULAR FUNCTION IN PATIENTS WITH LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE: A COMPARISON OF FUNCTIONS IN UPPER AND LOWER EXTREMITIES.

Peripheral arterial disease (PAD) is caused by atherosclerosis. Assessment of endothelial function in patients with PAD has been limited to that in forearm circulation in previous studies. The purpose of this study was to evaluate vascular function in upper and lower extremities in patients with PAD and to determine the relationship between the ankle-brachial pressure index (ABPI) and endothelial function in forearm and leg circulation. Forearm blood flow (FBF) and leg blood flow (LBF) responses to reactive hyperemia and sublingual administration of nitroglycerin (NTG) were measured using strain-gauge plethysmography in 57 PAD patients and 24 control patients. LBF during reactive hyperemia was significantly less in PAD patients than in control patients ($p < 0.001$). FBF during reactive hyperemia in PAD patients was similar to that in control patients. NTG-induced vasodilation in upper and lower extremities was similar in the two groups. There was a significant relationship between the maximal LBF response to reactive hyperemia and the ABPI in both the patients with PAD and control patients ($r = 0.384$, $p < 0.001$), whereas maximal FBF response to reactive hyperemia was not correlated with ABPI ($r = 0.182$, $p = 0.12$). These findings suggest that LBF response to reactive hyperemia is impaired in PAD patients compared with that in control patients. Impairment of vascular reactivity of leg circulation may occur before impairment of vascular reactivity of forearm circulation in PAD patients and may be a better indicator of the degree of PAD than impairment of vascular reactivity of forearm circulation.

Atherosclerosis. 2005 Jan;178(1):179-85

CIRCULATING ENDOTHELIAL PROGENITOR CELLS ARE REDUCED IN PERIPHERAL VASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS.

OBJECTIVES: We sought to establish whether a reduction in endothelial progenitor cells (EPCs) has a putative role in peripheral vascular disease (PVD) of type 2 diabetic patients. **BACKGROUND:** Peripheral vascular disease is a common and severe complication of diabetes mellitus. Impaired collateralization of diabetic vasculopathy has been extensively shown, but causes leading to its pathogenesis are not fully understood. Recently, EPCs have been found to contribute to vascular repair and angiogenesis. Diabetes has been associated with low levels of circulating EPCs, but no data are available in the literature on the relationship between EPCs and PVD in diabetes. **METHODS:** Flow cytometric analysis was used to quantify circulating progenitor cells (CPCs, CD34+) and EPCs (CD34+KDR+) in 51 patients and 17 control subjects. **RESULTS:** The CPCs and EPCs from diabetic patients were reduced by 33% and 40%, respectively, compared with healthy subjects ($p < 0.001$). An inverse correlation was found between the number of EPCs and the values of fasting glucose ($r = -0.49$, $p = 0.006$). Peripheral vascular disease was associated with a 47% reduction in EPCs ($p < 0.0001$) and EPC levels directly correlated with the ankle-brachial index ($r = 0.70$, $p = 0.01$). The subgroup of diabetic patients with PVD also had reduced CPCs by 32% ($p = 0.037$), whereas patients with ischemic foot lesions had the lowest levels of both EPCs and CPCs ($p = 0.02$). **CONCLUSIONS:** Our data demonstrate decreased EPC levels in diabetic patients and, for the first time, show that PVD is associated with an extensively low number of EPCs. Depletion of circulating EPCs in diabetic patients may be involved in the pathogenesis of peripheral vascular complications.

J Am Coll Cardiol. 2005 May 3;45(9):1449-57

MORBIDITY AND MORTALITY IN TYPE 1 AND TYPE 2 DIABETES MELLITUS AFTER THE DIAGNOSIS OF DIABETIC RETINOPATHY.

One to ten years after laser coagulation for diabetic retinopathy, 229 type I diabetics (mean age 44.3 years) and 157 type II diabetics (mean age 65 years) were re-studied for morbidity and mortality (progression of late damage, duration of survival, cause of death). The duration of diabetes at the first laser coagulation averaged 23.1 years for type I diabetics (15.9 years for type II). Average period from the first laser coagulation to the re-examination was 6.5 years for type I, 5.1 for type II diabetics. Of those patients still alive 6.7% had gone blind (type II: 7.3%). 2.1% and 4.6%, respectively, were receiving dialysis treatment, while renal transplantation had been performed in 3.1 and 1.8%, respectively. Stroke was the most frequent macrovascular complications (8.4 and 16.5%), followed by leg amputation (3.6 and 14.7%) and myocardial infarction (3.7 and 18.3%). 83 patients had died: 35 (15.3%) type I and 48 (30.6%) type II diabetics. Causes of death were septicaemia 14.3% (0%), uraemia 11.4% (8.3%), myocardial infarction 14.3% (33.3%), heart failure 8.6% (29.2%) and stroke 5.7% (6.3%). 10.7% (24.2%) had died within the first 5 years after laser coagulation. Despite a lower incidence of blindness in patients with diabetic retinopathy, the vascular disease progresses in other vascular regions so that a large proportion of diabetics will develop renal failure or die early from macrovascular complications.

Dtsch Med Wochenschr. 1992 Nov 6;117(45):1703-8

GREEN TEA CONSUMPTION AND MORTALITY DUE TO CARDIOVASCULAR DISEASE, CANCER, AND ALL CAUSES IN JAPAN: THE OHSAKI STUDY.

CONTEXT: Green tea polyphenols have been extensively studied as cardiovascular disease and cancer chemopreventive agents in vitro and in animal studies. However, the effects of green tea consumption in humans remain unclear. **OBJECTIVE:** To investigate the associations between green tea consumption and all-cause and cause-specific mortality. **DESIGN, SETTING, AND PARTICIPANTS:** The Ohsaki National Health Insurance Cohort Study, a population-based, prospective cohort study initiated in 1994 among 40,530 Japanese adults aged 40 to 79 years without history of stroke, coronary heart disease, or cancer at baseline. Participants were followed up for up to 11 years (1995-2005) for all-cause mortality and for up to 7 years (1995-2001) for cause-specific mortality. **MAIN OUTCOME MEASURES:** Mortality due to cardiovascular disease, cancer, and all causes. **RESULTS:** Over 11 years of follow-up (follow-up rate, 86.1%), 4,209 participants died, and over 7 years of follow-up (follow-up rate, 89.6%), 892 participants died of cardiovascular disease and 1,134 participants died of cancer. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. The inverse association with all-cause mortality was stronger in women ($P = .03$ for interaction with sex). In men, the multivariate hazard ratios of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.93 (95% confidence interval [CI], 0.83-1.05) for 1 to 2 cups/d, 0.95 (95% CI, 0.85-1.06) for 3 to 4 cups/d, and 0.88 (95% CI, 0.79-0.98) for 5 or more cups/d, respectively ($P = .03$ for trend). The corresponding data for women were 1.00, 0.98 (95% CI, 0.84-1.15), 0.82 (95% CI, 0.70-0.95), and 0.77 (95% CI, 0.67-0.89), respectively ($P < .001$ for trend). The inverse association with cardiovascular disease mortality was stronger than that with all-cause mortality. This inverse association was also stronger in women ($P = .08$ for interaction with sex). In women, the multivariate hazard ratios of cardiovascular disease mortality across increasing green tea consumption categories were 1.00, 0.84 (95% CI, 0.63-1.12), 0.69 (95% CI, 0.52-0.93), and 0.69 (95% CI, 0.53-0.90), respectively ($P = .004$ for trend). Among the types of cardiovascular disease mortality, the strongest inverse association was observed for stroke mortality. In contrast, the hazard ratios of cancer mortality were not significantly different from 1.00 in all green tea categories compared with the lowest-consumption category. **CONCLUSION:** Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer.

JAMA. 2006 Sep 13;296(10):1255-65

CIRCULATING OXIDIZED LOW-DENSITY LIPOPROTEIN IS AN INDEPENDENT PREDICTOR FOR CARDIAC EVENT IN PATIENTS WITH CORONARY ARTERY DISEASE.

Oxidized low-density lipoprotein (oxLDL) plays a crucial role in the development of atherosclerosis, however, the predictive value of circulating oxLDL for cardiac events (CE) in patients with coronary artery disease (CAD) has remained poorly understood. We prospectively studied 238 consecutive patients with documented CAD for up to 52 months until the occurrence of one of the following cardiac events: cardiac death, nonfatal myocardial infarction (MI), and refractory angina requiring revascularization. The plasma levels of oxLDL were measured by an enzyme-linked immunosorbent assay (ELISA) using the monoclonal antibody, DLH3. The levels of circulating oxLDL were significantly higher in patients with CE than in patients without CE (median 20.3 U/ml versus 17.6 U/ml, $P = 0.002$). Multivariate Cox models showed that higher level of oxLDL was an independent predictor of developing CE. The adjusted hazard ratios for CE were 3.15 (95% CI 1.47-6.76, $P = 0.003$) times higher in patients with the highest quartile of oxLDL levels and 1.88 (95% CI 0.90-3.95, $P = 0.09$) times higher in patients with the third quartile than in those within the lowest quartile. Thus, measurement of circulating oxLDL may be helpful in the assessment of future CE in patients with CAD.

Atherosclerosis. 2004 Jun;174(2):343-7

THE METABOLIC SYNDROME, CIRCULATING OXIDIZED LDL, AND RISK OF MYOCARDIAL INFARCTION IN WELL-FUNCTIONING ELDERLY PEOPLE IN THE HEALTH, AGING, AND BODY COMPOSITION COHORT.

The object of this study was to establish the association between the metabolic syndrome and oxidized LDL (oxLDL) and to determine the risk for coronary heart disease (CHD) in relation to the metabolic syndrome and levels of oxLDL. OxLDL was measured in plasma from 3,033 elderly participants in the Health, Aging, and Body Composition study. The metabolic syndrome was defined according to criteria established in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. We observed that the metabolic syndrome was

associated with higher levels of oxLDL due to a higher fraction of oxLDL, not to higher levels of LDL cholesterol. Individuals with the metabolic syndrome had twice the odds of having high oxLDL (>1.90 mg/dl) compared with those not having the metabolic syndrome, after adjusting for age, sex, ethnicity, smoking status, and LDL cholesterol. Among those participants who had the metabolic syndrome at study entry, incidence rates of future CHD events were 1.6-fold higher, after adjusting for age, sex, ethnicity, and smoking status. OxLDL was not an independent predictor of total CHD risk. However, those with high oxLDL showed a greater disposition to myocardial infarction (relative risk 2.25, 95% confidence interval 1.22-4.15). We concluded that the metabolic syndrome, a risk factor for CHD, is associated with higher levels of circulating oxLDL that are associated with a greater disposition to atherothrombotic coronary disease.

Diabetes. 2004 Apr;53(4):1068-73

ASSOCIATIONS AMONG OXIDIZED LOW-DENSITY LIPOPROTEIN ANTIBODY, C-REACTIVE PROTEIN, INTERLEUKIN-6, AND CIRCULATING CELL ADHESION MOLECULES IN PATIENTS WITH UNSTABLE ANGINA PECTORIS.

Oxidized low-density lipoprotein (LDL) is believed to play a key role in the development of atherosclerosis. However, the significance of anti-oxidized LDL antibody in atherogenesis is unclear. The purposes of this study were to assess whether anti-oxidized LDL antibody titers are related to other inflammatory markers of possible interest in atherosclerotic development, such as soluble cell adhesion molecules, interleukin-6, and C-reactive protein (CRP), and to determine the prognostic value of anti-oxidized LDL antibody as a predictor of cardiac events in patients with unstable angina pectoris. Sixty patients (35 men and 25 women; mean age 60 years) with unstable angina were included in this study. The levels of CRP and of intercellular adhesion molecule-1 (ICAM-1) at 24 and 72 hours after admission were significantly higher than their baseline levels ($p < 0.05$, respectively). After adjusting for age, gender, body mass index, and statin use, anti-oxidized LDL antibodies were positively correlated with CRP ($r = 0.72$, $p < 0.001$) and ICAM-1 ($r = 0.68$, $p < 0.001$). Elevated anti-oxidized LDL antibodies (mean >11.37 U/ml) and CRP levels (median >2.4 mg/L) on admission were correlated with a significantly lower 16-month, event-free survival rate (Kaplan-Meier event-free survival analysis, log-rank $p < 0.01$ and $p < 0.05$, respectively). Multivariate analysis by logistic regression revealed that elevated levels of anti-oxidized LDL antibody (mean >11.3 U/ml) on admission were an independent risk factor for an adverse cardiac event (odds ratio 2.2, 95% confidence interval 1.5 to 10.7, $p = 0.001$). This study demonstrates that anti-oxidized LDL antibody expression is associated with the expression of CRP and adhesion molecules, especially ICAM-1, and is a predictor of cardiac events in patients with unstable angina pectoris. The observed elevated levels of anti-oxidized LDL antibody suggest plaque instability and may be useful for identifying patients at higher risk of a cardiac event.

Am J Cardiol. 2004 Mar 1;93(5):554-8

RELATION BETWEEN ANTIBODY AGAINST OXIDIZED LOW-DENSITY LIPOPROTEIN AND EXTENT OF CORONARY ATHEROSCLEROSIS.

BACKGROUND AND PURPOSE: The role of antibody against oxidized low-density lipoprotein (Ab-ox-LDL) in acute myocardial infarction (AMI) and coronary artery disease (CAD) has not been fully elucidated. This study investigated the relationship between Ab-ox-LDL titers and the extent of coronary atherosclerosis, and determined the clinical significance of this antibody in AMI. **METHODS:** A total of 70 patients with significant coronary atherosclerosis demonstrated by coronary angiography were recruited. These patients were divided into AMI ($n = 33$; mean age, 63 yr; 29 men) and chronic stable CAD ($n = 37$; mean age, 62 yr; 30 men) groups. Serum Ab-ox-LDL was measured using an enzyme-linked immunosorbent assay. The extent of coronary atherosclerosis was assessed by an angiographic diffuse score system. **RESULTS:** In all patients, Ab-ox-LDL was significantly correlated with white blood cell count ($r = 0.309$; $p = 0.009$), but not with lipid profile or the diffuse score. Ab-ox-LDL (422.0 +/- 60.4 vs. 263.8 +/- 30.2 U/L; $p = 0.018$), white blood cell count (9,742 +/- 457 vs. 7,211 +/- 327/mm³; $p < 0.001$), and C-reactive protein (10.5 +/- 3.1 vs. 2.9 +/- 0.5 mg/L; $p = 0.022$) were significantly higher in patients with AMI than in those with chronic CAD. Peak creatine kinase concentration was significantly correlated with Ab-ox-LDL ($r = 0.499$; $p = 0.003$) among patients with AMI. **CONCLUSION:** Ab-ox-LDL is higher in patients with AMI and is correlated with myocardial damage to a greater degree than with the severity of coronary atherosclerosis and lipid profiles.

J Formos Med Assoc. 2002 Oct;101(10):681-4

THE AUTOANTIBODY EXPRESSION AGAINST DIFFERENT SOURCE OF OXIDIZED LOW DENSITY LIPOPROTEIN IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION.

The aim of this study was to examine the expression of antibodies against two different sources of low density lipoprotein (LDL) that were oxidized by CuSO₄, in patients with early stage of acute myocardial infarction (AMI). When LDL purified from sera with high level of LDL was used as a modified antigen, the results indicated that the titers of antibodies against the oxidized LDL in 30 patients were increased by 135% compared to those in normal subjects; however, the titers of antibody against modified LDL purified from normal-range LDL in the same patients were only slightly increased by 52%. Comparing the levels of autoantibody expressed in the high LDL sera group, high triglyceride sera group, and AMI patients sera group (total of 41; in

addition to 30 AMI patients, 11 more sera of AMI patients were collected), the amount of autoantibody against the oxLDL purified from high LDL sera in AMI patients sera group was significantly increased up to 195%. In contrast to AMI patients, the sera titers against the same antigen in two subject groups with either high LDL or high triglyceride are only 50% higher than normal subjects. Moreover, the ratio of thromboxane B(2) over 6-keto-prostaglandin F(1alpha) (6-keto-PG F(1alpha)) in the acute myocardial infarction patients was 1.79, which is much lower than the normal subjects, 4.19. Concluding from the above observations, we suggest that the expression level of anti-oxidized LDL antibody may play a role on the pathogenesis of acute myocardial infarction disease, but is independent with the levels of thromboxane A(2) and prostacyclin in the examined sera.

Thromb Res. 2002 Aug 15;107(3-4):175-9

MECHANICAL SIGNALS, IGF-I GENE SPLICING, AND MUSCLE ADAPTATION.

Combining physiological and molecular biology methods made it possible to identify and characterize a local muscle growth/repair factor (MGF). Following resistance exercise, MGF "kick starts" muscle hypertrophy and is important in local tissue repair. Loss of muscle mass in old age and certain diseases is associated with an impaired ability to express MGF.

Physiology (Bethesda). 2005 Aug;20:232-8

FATTY ACIDS AS MODULATORS OF THE IMMUNE RESPONSE.

Research describing fatty acids as modulators of inflammation and immune responses abounds. Many of these studies have focused on one particular group of fatty acids, omega-3. The data from animal studies have shown that these fatty acids can have powerful anti-inflammatory and immunomodulatory activities in a wide array of diseases (e.g., autoimmunity, arthritis, and infection). However, the evidence from human trials is more equivocal. In this review, a historical framework for understanding how and why fatty acids may affect the immune system is provided. Second, highlights of two recent landmark reports from the Agency for Healthcare Research and Quality are presented. These reports critically evaluate the evidence from human clinical trials of omega-3 fatty acids and rheumatoid arthritis, asthma, and a few other immune-mediated diseases. Third, the data from human clinical trials investigating the impact of various bioactive fatty acids on ex vivo and in vivo immune response are reviewed. Limitations in experimental design and immune assays commonly used are discussed. The discordance between expectation and evidence in this field has been a disappointment. Recommendations for improving both animal-based and human studies are provided.

Annu Rev Nutr. 2006;26:45-73

CLINICAL ANTICACHEXIA TREATMENTS.

Cachexia involves progressive loss of adipose tissue and skeletal muscle mass and is common in a number of end-stage diseases. Cachexia causes weakness and immobility, reduces the quality of life of the patient, and eventually results in death. We reviewed the medical literature concentrating upon agents that have undergone clinical evaluation for the treatment of patients with cachexia. These agents are discussed, together with their mechanisms of action. Megestrol acetate, corticosteroids, eicosapentaenoic acid, and thalidomide have shown some success in the treatment of cachexia. beta-hydroxy-beta-methylbutyrate, cyclooxygenase inhibitors, adenosine 5'-triphosphate, and growth hormone are undergoing clinical evaluation. Appetite stimulants such as cannabinoids and antisero-tonic agents have been shown to be ineffective in preventing progressive weight loss in cachexia. Much of the success in the treatment of cachexia has come from agents capable of blocking protein degradation through the ubiquitin-proteasome proteolytic pathway. Muscle mass can be increased when such agents are combined with agents that stimulate protein synthesis. In order to develop new agents, more fundamental research is required on the cellular mechanisms governing protein synthesis and degradation in skeletal muscle in cachexia.

Nutr Clin Pract. 2006 Apr;21(2):168-74

VITAMIN D IN THE AGING MUSCULOSKELETAL SYSTEM: AN AUTHENTIC STRENGTH PRESERVING HORMONE.

Until recently, vitamin D was only considered as one of the calcitrophic hormones without major significance in other metabolic processes in the body. Several recent findings have demonstrated that vitamin D plays also a role as a factor for cell differentiation, function and survival. Two organs, muscle and bone, are significantly affected by the presence, or absence, of vitamin D. In bone, vitamin D stimulates bone turnover while protecting osteoblasts of dying by apoptosis whereas in muscle vitamin D maintains the function of type II fibers preserving muscle strength and preventing falls. Furthermore, two major changes associated to aging: osteoporosis and sarcopenia, have been also linked to the development of frailty in elderly patients. In both cases vitamin D plays an important role since the low levels of this vitamin seen in senior people may be associated to a deficit in bone formation and muscle function. In this review, the interaction between vitamin D and the musculoskeletal components of frailty are considered from the basic mechanisms to the potential therapeutic approach. We expect that these new considerations about the importance of vitamin D in the elderly will stimulate an innovative approach to the problem of falls and fractures which constitutes a significant burden to public health budgets worldwide.

EXPRESSION OF IGF-I SPLICE VARIANTS IN YOUNG AND OLD HUMAN SKELETAL MUSCLE AFTER HIGH RESISTANCE EXERCISE.

The mRNA expression of two splice variants of the insulin-like growth factor-I (IGF-I) gene, IGF-IEa and mechano growth factor (MGF), were studied in human skeletal muscle. Subjects (eight young, aged 25-36 years, and seven elderly, aged 70-82 years) completed 10 sets of six repetitions of single legged knee extensor exercise at 80 % of their one repetition maximum. Muscle biopsy samples were obtained from the quadriceps muscle of both the control and exercised legs 2.5 h after completion of the exercise bout. Expression levels of the IGF-I mRNA transcripts were determined using real-time quantitative RT-PCR with specific primers. The resting levels of MGF were significantly (approximately 100-fold) lower than those of the IGF-IEa isoform. No difference was observed between the resting levels of the two isoforms between the two subject groups. High resistance exercise resulted in a significant increase in MGF mRNA in the young, but not in the elderly subjects. No changes in IGF-IEa mRNA levels were observed as a result of exercise in either group. The mRNA levels of the transcription factor MyoD were greater at rest in the older subjects ($P < 0.05$), but there was no significant effect of the exercise bout. Electrophoretic separation of myosin heavy chain (MHC) isoforms showed the older subjects to have a lower ($P < 0.05$) percentage of MHC-II isoforms than the young subjects. However, no association was observed between the composition of the muscle and changes in the IGF-I isoforms with exercise. The data from this study show an attenuated MGF response to high resistance exercise in the older subjects, indicative of age-related desensitivity to mechanical loading. The data in young subjects indicate that the MGF and IGF-IEa isoforms are differentially regulated in human skeletal muscle.

J Physiol. 2003 Feb 15;547(Pt 1):247-54

THE EFFECT OF RECOMBINANT HUMAN GROWTH HORMONE AND RESISTANCE TRAINING ON IGF-I MRNA EXPRESSION IN THE MUSCLES OF ELDERLY MEN.

The expression of two isoforms of insulin-like growth factor-I (IGF-I): mechano growth factor (MGF) and IGF-IEa were studied in muscle in response to growth hormone (GH) administration with and without resistance training in healthy elderly men. A third isoform, IGF-IEb was also investigated in response to resistance training only. The subjects (age 74 +/- 1 years, mean +/- S.E.M) were assigned to either resistance training with placebo, resistance training combined with GH administration or GH administration alone. Real-time quantitative RT-PCR was used to determine mRNA levels in biopsies from the vastus lateralis muscle at baseline, after 5 and 12 weeks in the three groups. GH administration did not change MGF mRNA at 5 weeks, but significantly increased IGF-IEa mRNA (237%). After 12 weeks, MGF mRNA was significantly increased (80%) compared to baseline. Five weeks of resistance training significantly increased the mRNA expression of MGF (163%), IGF-IEa (68%) and IGF-IEb (75%). No further changes were observed after 12 weeks. However, after 5 weeks of training combined with GH treatment, MGF mRNA increased significantly (456%) and IGF-IEa mRNA by (167%). No further significant changes were noted at 12 weeks. The data suggest that when mechanical loading in the form of resistance training is combined with GH, MGF mRNA levels are enhanced. This may reflect an overall up-regulation of transcription of the IGF-I gene prior to splicing.

J Physiol. 2004 Feb 15;555(Pt 1):231-40

TESTOSTERONE SUPPLEMENTATION THERAPY FOR OLDER MEN: POTENTIAL BENEFITS AND RISKS.

Serum testosterone levels decline gradually and progressively with aging in men. Many manifestations associated with aging in men, including muscle atrophy and weakness, osteoporosis, reduced sexual functioning, and increased fat mass, are similar to changes associated with testosterone deficiency in young men. These similarities suggest that testosterone supplementation may prevent or reverse the effects of aging. A MEDLINE search was performed to identify studies of testosterone supplementation therapy in older men. A structured, qualitative review was performed of placebo-controlled trials that included men aged 60 and older and evaluated one or more physical, cognitive, affective, functional, or quality-of-life outcomes. Studies focusing on patients with severe systemic diseases and hormone deficiencies related to specific diseases were excluded. In healthy older men with low-normal to mildly decreased testosterone levels, testosterone supplementation increased lean body mass and decreased fat mass. Upper and lower body strength, functional performance, sexual functioning, and mood were improved or unchanged with testosterone replacement. Variable effects on cognitive function were reported, with improvements in some cognitive domains (e.g., spatial, working, and verbal memory). Testosterone supplementation improved exercise-induced coronary ischemia in men with coronary heart disease, whereas angina pectoris was improved or unchanged. In a few studies, men with low testosterone levels were more likely to experience improvements in lumbar bone mineral density, self-perceived functional status, libido, erectile function, and exercise-induced coronary ischemia with testosterone replacement than men with less marked testosterone deficiency. No major unfavorable effects on lipids were reported, but hematocrit and prostate specific antigen levels often increased. Based on these results, testosterone supplementation cannot be recommended at this time for older men with normal or low-normal testosterone levels and no clinical manifestations of hypogonadism. However, testosterone replacement may be warranted in older men with markedly decreased testosterone levels, regardless of symptoms, and in men

with mildly decreased testosterone levels and symptoms or signs suggesting hypogonadism. The long-term safety and efficacy of testosterone supplementation remain uncertain. Establishment of evidence-based indications will depend on further demonstrations of favorable clinical outcomes and symptomatic, functional, and quality-of-life benefits in carefully performed, long-term, randomized, placebo-controlled clinical trials.

J Am Geriatr Soc. 2003 Jan;51(1):101-15

CREATINE SUPPLEMENTATION ENHANCES ISOMETRIC STRENGTH AND BODY COMPOSITION IMPROVEMENTS FOLLOWING STRENGTH EXERCISE TRAINING IN OLDER ADULTS.

We sought to determine whether creatine monohydrate (CrM) supplementation would enhance the increases in strength and fat-free mass that develop during resistance exercise training in older adults. Twenty-eight healthy men and women over the age of 65 years participated in a whole-body resistance exercise program 3 days per week for 14 weeks. The study participants were randomly allocated, in a double-blind fashion, to receive either CrM (5 g/d + 2 g of dextrose; n = 14) or placebo (7 g of dextrose; n = 14). The primary outcome measurements included the following: total body mass, fat-free mass, one-repetition maximum strength for each body part, isometric knee extension, handgrip, and dorsiflexion strength, chair stand performance, 30-m walk test, 14-stair climb performance, muscle fiber type and area, and intramuscular total creatine. Fourteen weeks of resistance exercise training resulted in significant increases in all measurements of strength and functional tasks and muscle fiber area for both groups ($p < .05$). CrM supplementation resulted in significantly greater increases in fat-free mass and total body mass, as compared with placebo ($p < .05$). The CrM group also showed a greater increase in isometric knee extension strength in men and women, as compared with placebo ($p < .05$), and also greater gains in isometric dorsiflexion strength ($p < .05$), but in men only. There was a significant increase in intramuscular total creatine in the CrM group ($p < .05$). Finally, there were no significant side effects of treatment or exercise training. This study confirms that supervised heavy resistance exercise training can safely increase muscle strength and functional capacity in older adults. The addition of CrM supplementation to the exercise stimulus enhanced the increase in total and fat-free mass, and gains in several indices of isometric muscle strength.

J Gerontol A Biol Sci Med Sci. 2003 Jan;58(1):11-9

SARCOPENIA OF AGING AND ITS METABOLIC IMPACT.

Sarcopenia contributes significantly to the morbidity, decrease in quality of life, and health care costs in the elderly. It is characterized by a decrease in muscle mass and strength, starting as early as the fourth decade of life in humans. Distinct muscle changes include a decrease in type 2 muscle fibers and a decrease in myosin heavy chains IIa and IIx mRNA levels. In addition, a decrease in whole body protein turnover, mixed muscle protein synthesis, myosin heavy chain synthesis, and mitochondrial protein synthesis have been reported. Different tissues and organs display different responses to aging, with more oxidative tissue generally having more age-related changes. Exercise has been shown to increase strength, aerobic capacity, and muscle protein synthesis, as well as to increase muscle mitochondrial enzyme activity in both young and older people; however, exercise does not reverse all age-related changes. The metabolic effects of sarcopenia include a decrease in resting metabolic rate secondary to decreased fat-free mass and decreased physical activity, leading to a higher prevalence of insulin resistance, type 2 diabetes mellitus, dyslipidemia, and hypertension. The way in which age-related changes in hormone levels affect muscle remains to be fully understood. The effect of replacing those hormones on sarcopenia has led to some conflicting results, but further investigations are ongoing.

Curr Top Dev Biol. 2005;68:123-48

PHYTOTHERAPY FOR BENIGN PROSTATIC HYPERPLASIA.

OBJECTIVE: To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH). **DESIGN:** Randomized trials were identified searching MEDLINE (1966--1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic preparation alone or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators. **RESULTS:** A total of 44 studies of six phytotherapeutic agents (*Serenoa repens*, *Hypoxis rooperi*, *Secale cereale*, *Pygeum africanum*, *Urtica dioica*, *Curcubita pepo*) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. *Serenoa repens*, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking *Serenoa repens* reported greater improvement of urinary tract symptoms and flow measures. *Serenoa repens* decreased nocturia (weighted mean difference (WMD) = -0.76 times per evening; 95% CI = -1.22 to -0.32; n = 10 studies) and improved peak urine flow (WMD = 1.93 ml s(-1); 95% CI = 0.72 to 3.14, n = 8 studies). Men treated with *Serenoa repens* rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio of improvement = 1.72; 95% CI = 1.21 to 2.44, n = 8 studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. *Hypoxis rooperi* (n = 4 studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was -4.9 IPSS points (95% CI = -6.3 to -3.5, n = 2 studies) and the WMD for peak urine flow was 3.91 ml s(-1) (95% CI = 0.91 to 6.90, n = 4 studies). *Secale cereale* (n = 4 studies, 444 men) was found to modestly improve overall urological symptoms. *Pygeum africanum* (n = 17 studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving *Urtica dioica* and *Curcubita pepo* are limited although these agents may be effective combined with other plant extracts such as *Serenoa* and *Pygeum*. Adverse events due to phytotherapies were reported to be generally mild and infrequent. **CONCLUSIONS:** Randomized studies of *Serenoa repens*, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. *Serenoa repens* appears to be a useful option for improving lower urinary tract symptoms and flow measures. *Hypoxis rooperi* and *Secale cereale* also appear to improve BPH symptoms although the evidence is less strong for these products. *Pygeum africanum* has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of *Urtica dioica* or *Curcubita pepo* alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

Public Health Nutr. 2000 Dec;3(4A):459-72

SERENOA REPENS (PERMIXON) INHIBITS THE 5ALPHA-REDUCTASE ACTIVITY OF HUMAN PROSTATE CANCER CELL LINES WITHOUT INTERFERING WITH PSA EXPRESSION.

The phytotherapeutic agent *Serenoa repens* is an effective dual inhibitor of 5alpha-reductase isoenzyme activity in the prostate. Unlike other 5alpha-reductase inhibitors, *Serenoa repens* induces its effects without interfering with the cellular capacity to secrete PSA. Here, we focussed on the possible pathways that might differentiate the action of Permixon from that of synthetic 5alpha-reductase inhibitors. We demonstrate that *Serenoa repens*, unlike other 5alpha-reductase inhibitors, does not inhibit binding between activated AR and the steroid receptor-binding consensus in the promoter region of the PSA gene. This was shown by a combination of techniques: assessment of the effect of Permixon on androgen action in the LNCaP prostate cancer cell line revealed no suppression of AR and maintenance of PSA protein expression at control levels. This was consistent with reporter gene experiments showing that Permixon failed to interfere with AR-mediated transcriptional activation of PSA and that both testosterone and DHT were equally effective at maintaining this activity. Our results demonstrate that despite *Serenoa repens* effective inhibition of 5alpha-reductase activity in the prostate, it did not suppress PSA secretion. Therefore, we confirm the therapeutic advantage of *Serenoa repens* over other 5alpha-reductase inhibitors as treatment with the phytotherapeutic agent will permit the continuous use of PSA measurements as a useful biomarker for prostate cancer screening and for evaluating tumour progression.

Int J Cancer. 2005 Mar 20;114(2):190-4

EFFECT OF PERMIXON ON HUMAN PROSTATE CELL GROWTH: LACK OF APOPTOTIC ACTION.

BACKGROUND: Permixon, a phytotherapeutic agent derived from the saw palmetto or *Serenoa repens* plant, is a lipid/sterol extract that is believed to interfere with 5 α -reductase activity, thus inhibiting prostate growth. In this study, we investigated the magnitude and specificity of the effect of Permixon on cell proliferation and apoptosis in human prostate cancer cells. **METHODS:** The effect of Permixon was examined in androgen-independent PC-3 prostate cancer cells, androgen-sensitive LNCaP prostate cancer cells, and MCF-7 breast cancer cells in vitro. Cell growth, apoptosis induction, and cell proliferation was studied after exposure to Permixon at two concentrations (10 and 100 microg/ml). Cell proliferation and cell cycle progression were determined after 24 hr on the basis of (3)[H]-thymidine incorporation assay and flowcytometric analysis, respectively. Apoptosis induction was evaluated in treated and untreated cultures using the Hoescht staining and caspase-3 activation. **RESULTS:** Exposure of prostate and breast cancer cells to a high dose of Permixon (100 microg/ml) resulted in a significant decrease in the rate of cell growth; an effect that was not time-dependent and was not associated with cell cycle arrest. Permixon treatment (at either high or low dose) had no effect on apoptosis induction in prostate cancer cell lines ($P > 0.6$). Furthermore, in vitro Permixon was a weak inhibitor of 5 α -reductase activity type 2 in prostatic homogenates. **CONCLUSIONS:** The results indicate the ability of Permixon to affect prostate cancer cell growth without inducing apoptosis or cell cycle arrest. This effect was not prostate-specific and was only manifested at high concentrations of Permixon. Furthermore our findings indicate that Permixon is weak inhibitor of 5 α -reductase compared to finasteride. This study challenges previous evidence on the anti-growth effect of Permixon in the prostate and its ability to inhibit 5 α -reductase activity, while questioning apoptosis as a mechanism of action of this phytotherapeutic against prostate growth, a concept that may have therapeutic significance.

Prostate. 2004 Sep 15;61(1):73-80

TISSUE EFFECTS OF SAW PALMETTO AND FINASTERIDE: USE OF BIOPSY CORES FOR IN SITU QUANTIFICATION OF PROSTATIC ANDROGENS.

OBJECTIVES: To determine the effects of a saw palmetto herbal blend (SPHB) compared with finasteride on prostatic tissue androgen levels and to evaluate needle biopsies as a source of tissue for such determinations. **METHODS:** Prostate levels of testosterone and dihydrotestosterone (DHT) were measured on 5 to 10-mg biopsy specimens (18-gauge needle cores) in three groups of men with symptomatic benign prostatic hyperplasia: 15 men receiving chronic finasteride therapy versus 7 untreated controls; 4 men undergoing prostate adenectomy to determine sampling variability (10 specimens each); and 40 men participating in a 6-month randomized trial of SPHB versus placebo, before and after treatment. **RESULTS:** Prostatic tissue DHT levels were found to be several times higher than the levels of testosterone (5.01 versus 1.51 ng/g), that ratio becoming reversed (1.05 versus 3.63 ng/g) with chronic finasteride therapy. The finasteride effect was statistically significant for both androgens ($P < 0.01$), and little overlap of individual values between finasteride-treated and control patients was seen. In the randomized trial, tissue DHT levels were reduced by 32% from 6.49 to 4.40 ng/g in the SPHB group ($P < 0.005$), with no significant change in the placebo group. **CONCLUSIONS:** For control versus finasteride-treated men, the tissue androgen values obtained with needle biopsy specimens were similar-both for absolute values and the percentage of change-to those previously reported using surgically excised volumes of prostatic tissue. The quantification of prostatic androgens by assay of needle biopsies is thus feasible and offers the possibility of serial studies in individual patients. The SPHB-induced suppression of prostatic DHT levels, modest but significant in a randomized trial, lends an element of support to the hypothesis that inhibition of the enzyme 5- α reductase is a mechanism of action of this substance.

Urology. 2001 May;57(5):999-1005

SAW PALMETTO FOR THE TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS.

PURPOSE: A comprehensive review of the literature on the use of saw palmetto in men with lower urinary tract symptoms is provided. **MATERIALS AND METHODS:** A literature search of studies that have assessed the mechanism of action and clinical results of saw palmetto in men with benign prostatic hyperplasia was performed. **RESULTS:** A variety of potential mechanisms of action of saw palmetto have been demonstrated through in vitro studies, including 5- α reductase inhibition, adrenergic receptor antagonism and intraprostatic androgen receptor blockade. Clinical evidence of the relevance of these effects is largely unavailable. The use of saw palmetto in men with benign prostatic hyperplasia is safe with no recognized adverse effects. No effect on serum prostate specific antigen has been noted. Placebo controlled trials and meta-analyses have suggested that saw palmetto leads to subjective and objective improvement in men with lower urinary tract symptoms. However, most studies are significantly limited by methodological flaws, small patient numbers and brief treatment intervals. **CONCLUSIONS:** Evidence suggests that saw palmetto may have a significant effect on urinary flow rates and symptom scores compared to placebo in men with lower urinary tract symptoms. However, large scale, placebo controlled trials are needed to assess the efficacy of saw palmetto.

J Urol. 2000 May;163(5):1408-12

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO DETERMINE THE EFFECTIVENESS OF BOTANICALLY DERIVED INHIBITORS OF 5-ALPHA-REDUCTASE IN THE TREATMENT OF ANDROGENETIC ALOPECIA.

BACKGROUND: Androgenetic alopecia (AGA) is characterized by the structural miniaturization of androgen-sensitive hair follicles in susceptible individuals and is anatomically defined within a given pattern of the scalp. Biochemically, one contributing factor of this disorder is the conversion of testosterone (T) to dihydrotestosterone (DHT) via the enzyme 5-alpha reductase (5AR). This metabolism is also key to the onset and progression of benign prostatic hyperplasia (BPH). Furthermore, AGA has also been shown to be responsive to drugs and agents used to treat BPH. Of note, certain botanical compounds have previously demonstrated efficacy against BPH. Here, we report the first example of a placebo-controlled, double-blind study undertaken in order to examine the benefit of these botanical substances in the treatment of AGA. **OBJECTIVES:** The goal of this study was to test botanically derived 5AR inhibitors, specifically the liposterolic extract of *Serenoa repens* (LSESr) and beta-sitosterol, in the treatment of AGA. **Subjects:** Included in this study were males between the ages of 23 and 64 years of age, in good health, with mild to moderate AGA. **RESULTS:** The results of this pilot study showed a highly positive response to treatment. The blinded investigative staff assessment report showed that 60% of (6/10) study subjects dosed with the active study formulation were rated as improved at the final visit. **CONCLUSIONS:** This study establishes the effectiveness of naturally occurring 5AR inhibitors against AGA for the first time, and justifies the expansion to larger trials.

J Altern Complement Med. 2002 Apr;8(2):143-52

SAW PALMETTO AND BENIGN PROSTATIC HYPERPLASIA.

Benign prostatic hyperplasia (BPH) is a common health issue that affects 8% of all men at the age of 40, 60% of men in their 70s, and 90% of those greater than 80 years of age. One-fourth of these men will develop moderate to severe lower urinary tract symptoms that greatly affect their quality of life. Recent evidence suggests that the use of saw palmetto leads to improvements in urinary function for those suffering from BPH. The favorable comparison of saw palmetto with tamsulosin, a well-known first line agent in the treatment of urinary tract symptoms, demonstrates promise towards a beneficial effect of this herbal agent, with very few, if any, adverse effects. However, what degree of this beneficial activity is due to placebo effects is yet to be determined. In addition, the precise mechanism of action of saw palmetto in men with BPH remains unclear.

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