LE Magazine October 2005

ABSTRACTS

Peak ATP

EFFECT OF PROPIONYL-L-CARNITINE ON EXERCISE PERFORMANCE IN PERIPHERAL ARTERIAL DISEASE.

BACKGROUND: Supplemen tation with propionyl-L-car nitine (PLC) may be of use in improving the exercise capacity of people with peripheral arterial disease. METHODS: After a 2-wk exercise familiarization phase, seven subjects displaying intermittent claudication were studied over a 12-wk period consisting of three 4-wk phases, baseline (B), supplementation (S), and placebo (P). PLC was supplemented at 2 g x d(-1), and subjects were blinded to the order of supplementation. Unilateral calf strength and endurance were assessed weekly. Walking performance was assessed at the end of each phase using an incremental protocol, during which respiratory gases were collected. RESULTS: Although there was not a significant increase in maximal walking time (approximately 14%) in the whole group, walking time improved to a greater extent than the individual baseline coefficient of variation in four of the seven subjects. The changes in walking performance were correlated with changes in the respiratory exchange ratio both at steady state (r = 0.59) and maximal exercise (r = 0.79). Muscle strength increased significantly from 695 +/- 198 N to 812 +/- 249 N by the end of S. Changes in calf strength from B to S were modestly related to changes in walking performance (r = 0.56). No improvements in calf endurance were detected throughout the study. CONCLUSIONS: These preliminary data suggest that, in addition to walking performance, muscle strength can be increased in PAD patients after 4 wk of supplementation with propionyl-L-carnitine.

Med Sci Sports Exerc. 2001 Sep;33(9):1415-22

CARNITINE AND PERIPHERAL ARTERIAL DISEASE.

Patients with peripheral arterial disease (PAD) who become symptomatic with claudication (approximately one-third of the population) have a marked impairment in exercise performance and overall functional capacity. Patients with claudication have a peak oxygen consumption measured during graded treadmill exercise testing that is 50% of that in age-matched normal subjects, and also report great difficulty in walking relatively short distances, even at a slow walking speed. The reduced walking capacity is associated with impairment in activities of daily living and quality of life. Thus, claudication is highly limiting to the physical functioning of daily activities. Improving mobility and improving the reduced quality of life are therefore major goals of treatment. Patients with PAD develop metabolic abnormalities in the skeletal muscles of the lower extremity. These abnormalities include impairment in ischemic muscle mitochondrial electron transport chain activity and accumulation of intermediates of oxidative metabolism (acylcarnitines). Patients with the greatest accumulation of muscle acylcarnitines have the most impaired exercise performance. Thus, claudication is not simply the result of reduced blood flow, and alterations in skeletal muscle metabolism are part of the pathophysiology of the disease. L-carnitine and propionyl-L-carnitine may improve the metabolism and exercise performance of ischemic muscles. L-carnitine in a dose of 2 grams twice daily improved treadmill performance, but propionyl-L-carnitine (an acyl form of carnitine) was more effective than L-carnitine in improving treadmill walking distance. In two multicenter trials of a total of 730 patients, initial and maximal treadmill walking distance improved more with propionyl-L-carnitine than placebo. The drug also improved quality of life and had minimal side effects as compared with placebo. Propionyl-L-carnitine has not been approved for use in the United States .

Ann N Y Acad Sci. 2004 Nov;1033:92-8

EXPLORATORY OPEN LABEL, RANDOMIZED STUDY OF ACETYL- AND PROPIONYLCARNITINE IN CHRONIC FATIGUE SYNDROME.

OBJECTIVES: We compared the effects of acetylcarnitine, propionylcarnitine and both compounds on the symptoms of chronic fatigue syndrome (CFS). METHODS: In an open, randomized fashion we compared 2 g/d acetyl-L-carnitine, 2 g/d propionyl-L-carnitine, and its combination in 3 groups of 30 CFS patients during 24 weeks. Effects were rated by clinical global impression of change. Secondary endpoints were the Multidimensional Fatigue Inventory, McGill Pain Questionnaire, and the Stroop attention concentration test. Scores were assessed 8 weeks before treatment; at randomization; after 8, 16, and 24 weeks of treatment; and 2 weeks later. RESULTS: Clinical global impression of change after treatment showed considerable improvement in 59% of the patients in the acetylcarnitine group and 63% in the propionylcarnitine group, but less in the acetylcar nitine plus propionylcarnitine group (37%). Acetylcarnitine significantly improved mental fatigue (p =.015) and propionylcarnitine improved

general fatigue (p =.004). Attention concentration improved in all groups, whereas pain complaints did not decrease in any group. Two weeks after treatment, worsening of fatigue was experienced by 52%, 50%, and 37% in the acetylcarnitine, propionylcarnitine, and combined group, respectively. In the acetylcarnitine group, but not in the other groups, the changes in plasma carnitine levels correlated with clinical improvement. CONCLUSIONS: Acetylcarnitine and propionylcarnitine showed beneficial effect on fatigue and attention concentration. Less improvement was found by the combined treatment. Acetylcarnitine had main effect on mental fatigue and propionylcarnitine on general fatigue.

Psychosom Med. 2004 Mar-Apr;66(2):276-82

CARNITINE VERSUS ANDROGEN ADMINISTRATION IN THE TREATMENT OF SEXUAL DYSFUNCTION, DEPRESSED MOOD, AND FATIGUE ASSOCIATED WITH MALE AGING.

OBJECTIVES: To To compare testosterone undecanoate versus propionyl-L-carnitine plus acetyl-L-carnitine and placebo in the treatment of male aging symptoms. METHODS: A total of 120 patients were randomized into three groups. The mean patient age was 66 years (range 60 to 74). Group 1 was given testosterone undecanoate 160 mg/day, the second group was given propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group was given a placebo (starch). Drugs and placebo were given for 6 months. The assessed variables were total prostate-specific antigen, prostate volume, peak systolic velocity, end-diastolic velocity, resistive index of cavernosal penile arteries, nocturnal penile tumescence, total and free testosterone, prolactin, luteinizing hormone, International Index of Erectile Function score, Depression Melancholia Scale score, fatigue scale score, and incidence of side effects. The assessment was performed at intervals before, during, and after therapy. RESULTS: Testosterone and carnitines significantly improved the peak systolic velocity, end-diastolic velocity, resistive index, nocturnal penile tumescence, International Index of Erectile Function score, Depression Melancholia Scale score, and fatigue scale score. Carnitines proved significantly more active than testosterone in improving nocturnal penile tumescence and International Index of Erectile Function score. Testosterone significantly increased the prostate volume and free and total testosterone levels and significantly lowered serum luteinizing hormone; carnitines did not. No drug significantly modified prostate-specific antigen or prolactin. Carnitines and testosterone proved effective for as long as they were administered, with suspension provoking a reversal to baseline values. Only the group 1 prostate volume proved significantly greater than baseline 6 months after testosterone suspension. Placebo administration proved ineffective. Negligible side effects emerged. CONCLUSIONS: Testosterone and, especially, carnitines proved to be active drugs for the therapy of symptoms associated with male aging.

Urology. 2004 Apr;63(4):641-6

DIABETES MELLITUS AND SUBJECTS' AGEING: A STUDY ON THE ATP CONTENT AND ATP-RELATED ENZYME ACTIVITIES IN HUMAN ERYTHROCYTES.

Na+/K(+)- and Ca(2+)-ATPase are the major ATP-dependent membrane-bound enzymes that regulate the cation transmembrane gradient which is altered both in red blood cell (RBC) senescence and in RBCs of diabetic patients. In an attempt to clarify the possible connection between diabetes mellitus and ageing, we investigated the relationship between RBC ATP content, Na+/K(+)-ATPase, Ca(2+)-ATPase activities and ageing in healthy, insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) subjects. A significant correlation was found ($r = -0.82$; $P < 0.001$) between RBC ATP content and subject's age only in the control group. A significant reduction in Na+/K(+)-ATPase activity was observed in the older group (C2) of control subjects, in comparison with the younger (C1) one. In both IDDM and NIDDM subjects, the enzymatic activity was significantly decreased when compared with health subjects of similar age ($P < 0.001$). A significant negative correlation was found between age and enzymatic activity in healthy subjects ($r = -0.60$; $P < 0.001$). No difference was observed in the RBC membrane Ca(2+)-ATPase activity between younger (C1) and older (C2) healthy subjects. Ca(2+)-ATPase activity was significantly increased both in IDDM patients compared with C1 ($P < 0.001$) and in NIDDM patients compared with C2 ($P < 0.001$). The present data indicate that ageing causes a reduction in the erythrocyte ATP content in both healthy and diabetic subjects. In diabetic patients Na+/K(+)-ATPase activity decreases independently of age.

Eur J Clin Invest. 1997 Apr;27(4):327-32

CARDIOVASCULAR AND PULMONARY RESPONSE TO ORAL ADMINISTRATION OF ATP IN RABBITS.

Extracellular purines such as ATP and adenosine participate in the regulation of cardiovascular and respiratory functions through specific P1 and P2 purine receptors. These properties have mainly been described after intravenous infusion. Experiments reported herein were designed to explore the possible effect of oral ATP administration (3 or 20 mg. kg(-1). day(-1)) on vascular, cardiac, and pulmonary functions in rabbits. Whereas a unique oral dose of ATP has no effect, chronic supplementation during 14 days reduces peripheral vascular resistance, pulmonary resistance, and respiratory frequency and increases arterial PO (2). No effect on central blood pressure and heart rate is observed, but an increase of the left ventricular work index is noticed subsequent to the diminution of vascular resistance. Rather similar cardiovascular modifications are observed in rabbits given 20 mg. kg(-1). day(-1) adenosine for 14 days but without variation of respiratory parameters. These original effects of repeated oral treatment with ATP may result from an adaptive metabolic response to nucleoside supplementation that might affect the turnover

of extracellular purines leading to P1- and/or P2-receptor activation.

J Appl Physiol. 2000 Jun;88(6):1962-8

ABSTRACTS

Omega fish oil

TIME TREND INVESTIGATION OF PCBS, PBDES, AND ORGANOCHLORINE PESTICIDES IN SELECTED N-3 POLYUNSATURATED FATTY ACID RICH DIETARY FISH OIL AND VEGETABLE OIL SUPPLEMENTS; NUTRITIONAL RELEVANCE FOR HUMAN ESSENTIAL N-3 FATTY ACID REQUIREMENTS.

In addition to being used in the food and animal feed industry, fish oils have also been used traditionally as dietary supplements. Due to the presence of long-chain n-3 fatty acids, fish oils have therapeutic benefits in the prevention and treatment of cardiovascular, immunological, and arthritic diseases, as well as childhood deficiency diseases such as rickets, because of a high content of vitamin D. However, fish oils are also susceptible to contamination with lipophilic organic chemicals that are now ubiquitous contaminants of marine ecosystems. Many vegetable oils are sources of the shorter chain precursor forms of n-3 fatty acids, and in recent years the specialist dietary supplement market has expanded to include these oils in a variety of different formulations. This paper reports analytical results of selected contaminants, including polychlorinated biphenyls, organochlorine pesticides, and polybrominated diphenyl ethers, for a range of commercially available n-3 fatty acid rich fish and vegetable oil dietary supplements. Using principal component analysis, the values are compared with historic samples to elucidate time trends in contamination profiles. Levels of contaminants are discussed in relation to the nutritional benefits to the consumer of long- and short-chain forms of n-3 fatty acids.

J Agric Food Chem. 2004 Mar 24;52(6):1780-8

POLYCHLORINATED BIPHENYLS, HEXACHLOROBENZENE, HEXACHLOROCYCLOHEXANE ISOMERS, AND PESTICIDE ORGANOCHLORINE RESIDUES IN COD-LIVER OIL DIETARY SUPPLEMENTS.

Levels of polychlorinated biphenyls (PCBs), hexachlorobenzene, hexachlorocyclohexane isomers (alpha, beta, gamma), and chlorinated pesticides (DDTs) in cod-liver oil used as a dietary supplement were determined. Total PCB and DDT concentrations varied from 25 to 201 ng g(-1) lipid weight basis and from 25 to 133 ng g(-1) lipid weight basis, respectively. Hexachlorobenzene contributed very little to the overall contaminant burden of dietary supplement oils, whereas hexachlorocyclohexane isomers were below the instrumental detection limits in all samples. The daily intake of PCBs and DDTs derived by the consumption of cod-liver oil at manufacturer-recommended doses varied from 0.004 to 2.01 microg/day and from 0.004 to 1.24 microg/day, respectively. Relative to some dioxin-like PCB congeners (mono-ortho PCB 105, 118, and 156; non-ortho PCB 77, 126, and 169), the intakes calculated varied from less than 0.001 to 0.74 pg of toxic equivalency values (TEQ) per kg of body weight per day. These values, although below the range of 1 to 4 pg of TEQ per kg of body weight per day set by the World Health Organization, emphasize the need for strict and continuous monitoring of fish oil contamination to reduce the risks to human health.

J Food Prot. 2004 Aug;67(8):1787-91

POLYCHLORINATED BIPHENYL CONGENERS AS MARKERS OF TOXIC EQUIVALENTS OF POLYCHLORINATED BIPHENYLS, DIBENZO-P-DIOXINS AND DIBENZOFURANS IN BREAST MILK.

In breast milk, concentrations of polychlorinated biphenyls (PCBs) are higher than those of poly chlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs), making PCB analyses less time-consuming and expensive. We searched for PCB “markers” of PCDD/DF concentrations, by studying associations between concentrations of PCB and PCDD/DFs (expressed as toxic equivalents, TEQs) in breast milk from 27 women (primiparas, 22-35 years). These women donated breast milk in 1996-1999 together with 183 other primiparas from Uppsala County, Sweden . Regression analyses showed that both dioxin-like and non-dioxin-like penta- to hepta-chlorinated PCBs could be used as markers of TEQ concentrations in this group of women, in some cases after age adjustment of the regressions. The strong positive association between concentrations of dioxin-like PCB/DD/DFs and non-dioxin-like PCBs will in future epidemiological studies make it difficult to separate Ah receptor-dependent effects from non-Ah receptor-dependent effects. With the use of regression equations and concentrations in breast milk samples collected in 1994, TEQ concentrations were estimated in the 1994 samples. Comparisons between estimated and measured concentrations indicated that associations between concentrations of marker substances and TEQs should be determined separately within each study population, in order to obtain reliable TEQ exposure assessments from PCB markers.

Environ Res. 2001 Jul;86(3):217-28

GLOBAL ASSESSMENT OF ORGANIC CONTAMINANTS IN FARMED SALMON.

The annual global production of farmed salmon has increased by a factor of 40 during the past two decades. Salmon from farms in northern Europe, North America, and Chile are now available widely year-round at relatively low prices. Salmon farms have been criticized for their ecological effects, but the potential human health risks of farmed salmon consumption have not been examined rigorously. Having analyzed over 2 metric tons of farmed and wild salmon from around the world for organochlorine contaminants, we show that concentrations of these contaminants are significantly higher in farmed salmon than in wild. European-raised salmon have significantly greater contaminant loads than those raised in North and South America, indicating the need for further investigation into the sources of contamination. Risk analysis indicates that consumption of farmed Atlantic salmon may pose health risks that detract from the beneficial effects of fish consumption.

Science. 2004 Jan 9;303(5655):226-9

ABSTRACTS

Erectile dysfunction

NEW ORAL AGENTS FOR ERECTILE DYSFUNCTION: WHAT IS CHANGING IN OUR PRACTICE?

Erectile dysfunction (ED) is a highly prevalent disorder affecting an estimated 152 million men worldwide and is associated with a variety of behavioral risk factors, such as cigarette smoking and excessive alcohol consumption, as well as numerous age-related medical conditions, notably type-2 diabetes mellitus and cardiovascular disease. A rational step-wise approach which includes comprehensive medical and sexual history, a focused physical examination and essential laboratory tests such as fasting glucose, lipid profile and testosterone assay is to be preferred. Current diagnostic work-up does not recommend any of the specialized tests which were previously considered mandatory-i. e. penile pharmacotesting, Duplex ultrasound and nocturnal penile tumescence. Hormonal replacement therapy is appropriate only in the hypogonadal male with ED. Prior to direct intervention, the physician should consider altering modifiable risk factors or causes, although frequently insufficient to reverse ED completely. When indicated, oral therapy with new molecules (phosphodiesterase inhibitors or apomorphine) is the first-line treatment for the majority of patients because of potential benefits and lack of invasiveness.

Asian J Androl. 2001 Sep;3(3):175-9

NUTRIENTS AND BOTANICALS FOR ERECTILE DYSFUNCTION: EXAMINING THE EVIDENCE.

Erectile dysfunction affects 50% of men ages 40-70 in the United States and is considered an im portant public health problem by the National Institutes of Health. Consumers are exposed to a plethora of natural products claiming to restore erection and sexual vitality. A review of the available empirical evidence reveals most naturally occurring compounds lack adequate clinical trials to support efficacy. However, arginine, yohimbine, Panax ginseng, Maca, and Ginkgo biloba all have some degree of evidence they may be helpful for erectile dysfunction. Improve ments in penile endothelial L-arginine-nitric oxide activity appear to be a unifying explanation for the actions of these naturally occurring agents.

Altern Med Rev. 2004 Mar;9(1):4-16

NEURAL CONTROL OF ERECTION.

Activation of sacral parasympathetic pathways elicits penile erection through the release of vasorelaxant neurotransmitters that increase blood flow to the penis and relax the penile erectile tissue. Sympathetic pathways are antierectile. The pudendal pathway, responsible for the contraction of the perineal striated muscles, enhances an already present erection. All pathways originate in the spinal cord, but at various levels and areas. The convergence of information from peripheral and supra-spinal origins onto spinal neurones is very likely activating more specifically the spinal pro-erectile network. Peripheral information is the afferent limb of reflexive erections, impinges onto spinal interneurones and is able to activate or regulate the activity of sympathetic, parasympathetic and somatic nuclei. Supra-spinal information impinges onto either the same or a different spinal network. Premotor neurones located in supra-spinal structures, that project directly onto spinal sympathetic, parasympathetic or pudendal motoneurones, are present in the medulla, pons and diencephalon. Several of these premotor neurones may in turn be activated by sensory information from the genitals. Descending pathways release a variety of aminergic and peptidergic neurotransmitters in the vicinity of spinal neurones, thereby exerting complex effects on the spinal pro-erectile network. Brainstem and hypothalamic nuclei (among the latter, the paraventricular nucleus and the medial preoptic area) may not reach directly the spinal pro-erectile network. They are prone to regulate penile erection in more integrated and coordinated responses of the body, as those occurring during sexual behaviour. The pro-erectile central and spinal effects of neuropeptides such as oxytocin, melanocortins and endorphins have only recently been analyzed. Such compounds may represent therapeutic strategies to treat erectile dysfunction through a central site of action.

J Soc Biol. 2004; 198(3):217-30

THE EFFECTS OF SMOKING ON THE REPRODUCTIVE HEALTH OF MEN.

This article discusses the impact smoking can have on men’s sexual and reproductive health. There is evidence to suggest that smoking can result in alterations of the male sex hormones and is a key cause of and contributor to erectile dysfunction. Smoking can therefore endanger the man’s ability to have a family and enjoy sexual activity. A reduction in sperm quality and a reduced response to fertility treatments has also been linked with those men who smoke. The damaging effects of smoking are apparent throughout the lifespan of a smoker. The benefits associated with cessation of smoking are wide and varied with respect

to the reproductive health of men; these benefits can include a reduction in the risk of male impotence and an improvement in sexual potency.

Br J Nurs. 2005 Apr 14-27;14(7):362-6

CURRENT OPINIONS ON THE RELATIONSHIPS BETWEEN ATHERO-THROMBOSIS, TYPE 2 DIABETES MELLITUS AND ERECTILE DYSFUNCTION.

Erectile dysfunction is often associated with diabetes mellitus and athero-thrombotic diseases, such as coronary heart disease, stroke, peripheral vascular disease. An association between erectile dysfunction and asymptomatic coronary artery disease angiographically verified has been recently shown in diabetic patients. Several pathophysiological mechanisms may explain the relationship between erectile dysfunction and athero-thrombosis, especially in diabetic subjects. Among these mechanisms, it is of interest to consider a common pattern of cardiovascular risk factors, the presence of autonomic neuropathy and endothelial dysfunction. The strong association between erectile dysfunction and athero-thrombosis may have some important clinical implications. In particular, erectile dysfunction may be used as a predictor of silent or early athero-thrombotic diseases, especially in diabetic patients.

Recenti Prog Med. 2005 Mar;96(3):155-8

A DOUBLE BLIND, RANDOMISED STUDY OF SILDENAFIL CITRATE FOR ERECTILE DYSFUNCTION IN MEN WITH MULTIPLE SCLEROSIS.

OBJECTIVE: Identifying and effectively treating erectile dysfunction (ED) can result in an improvement of the quality of life (QoL) in men with multiple sclerosis (MS). METHODS: This randomised, double blind (DB), placebo controlled, flexible dose study with an open label extension (OLE) assessed efficacy, QoL, and safety of sildenafil citrate in men with MS and ED. Overall, 217 men received sildenafil (25-100 mg; n = 104) or placebo (n = 113) for 12 weeks. Efficacy was assessed by the International Index of Erectile Function (IIEF) questionnaire that includes questions on achieving (Q3) and maintaining (Q4) an erection as well as a global efficacy question (GEQ). QoL was also assessed. RESULTS: After 12 weeks, patients receiving sildenafil had higher mean scores for IIEF Q3 and Q4 compared with those receiving placebo ($p<0.0001$), and 89% (92/103) reported improved erections compared with 24% (27/112) of patients receiving placebo ($p<0.0001$). At the end of the OLE phase, 95% of men reported improved erections. Patients receiving placebo during the DB phase showed a nearly fourfold increase in improved erections (97% v 26%). Men receiving sildenafil also showed improvements in five of the eight general QoL questions compared with men receiving placebo ($p<0.05$). The total mean score for the QoL questionnaire improved by 43% for the sildenafil group versus 13% for the placebo group ($p<0.0001$). Treatment related AEs were predominantly mild in nature, and no patient discontinued due to an AE. CONCLUSION: Sildenafil treatment for ED in men with MS was effective and well tolerated, and resulted in significant improvements in both general and disease specific QoL variables.

J Neurol Neurosurg Psychiatry. 2005 May;76(5):700-5

SYMPTOMS OF AUTONOMIC FAILURE IN PARKINSON'S DISEASE: PREVALENCE AND IMPACT ON DAILY LIFE.

Frequency and clinical importance of autonomic failure in idiopathic Parkinson's disease (PD) are discussed controversially. 141 patients with PD and 50 healthy age-matched control subjects were interviewed for symptoms of autonomic failure and their influence on daily life using a questionnaire. In PD patients, the prevalence of orthostatic dizziness, bladder dysfunction, erectile dysfunction and hyperhidrosis was significantly higher compared with controls. About 50% of PD patients rated the impact of the symptoms of autonomic failure on their daily lives as "a lot" or "very much" due to orthostatic dizziness, bladder dysfunction and constipation, which were more statistically significant than in age-matched controls. Prevalence and number of autonomic symptoms were not correlated with duration and severity of PD. In 32% of patients, impaired cardiovascular regulation was found by standardized cardiovascular function tests. If testing showed abnormal findings, orthostatic dizziness, bladder dysfunction, constipation and erectile dysfunction were significantly more frequent than in patients with normal regulation, but the impact on daily life due to these symptoms differed significantly only for bladder dysfunction between groups. It is concluded that autonomic failure is a clinically relevant, pervasive problem in PD and compromise patients' daily life activities in all stages of the disease. This underlines the necessity to adequately search for and treat these non-dopaminergic symptoms during the whole course of the disease.

Clin Auton Res. 2005 Apr;15(2):76-82

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