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JOURNAL  
ABSTRACTS

## Mediterranean Diet

**ADHERENCE TO THE MEDITERRANEAN DIET IS INVERSELY ASSOCIATED WITH CIRCULATING INTERLEUKIN-6 AMONG MIDDLE-AGED MEN: A TWIN STUDY.**

**BACKGROUND:** The Mediterranean diet is protective against cardiovascular disease; a proposed mechanism is through a reduction in systemic inflammation. It is unknown to what extent the association between the Mediterranean diet and inflammation is due to genetic or other familial factors. **METHODS AND RESULTS:** We administered the Willett food frequency questionnaire to 345 middle-aged male twins and assessed adherence to the Mediterranean diet using a published adherence score. Fasting plasma levels of interleukin-6, C-reactive protein, and known cardiovascular risk factors were measured. Mixed-effect regression analyses were used to examine the relationship between diet score and inflammatory biomarkers after accounting for known cardiovascular risk factors. Adherence to the Mediterranean diet was associated with reduced levels of interleukin-6 ( $P < 0.001$ ) but not C-reactive protein ( $P = 0.10$ ) after adjustment for total energy intake, other nutritional factors, known cardiovascular risk factors, and use of supplements and medications. When the overall association of adherence to the diet with interleukin-6 levels was partitioned into between- and within-pair effects, the between-pair effect was not significant ( $P = 0.9$ ) and the within-pair effect was highly significant ( $P < 0.0001$ ). A 1-unit within-pair absolute difference in the diet score was associated with a 9% (95% CI, 4.5 to 13.6) lower interleukin-6 level. **CONCLUSIONS:** Shared environmental and genetic factors are unlikely to play a major role in the association between adherence to the Mediterranean diet and systemic inflammation. These results support the hypothesis that reduced inflammation is an important mechanism linking Mediterranean diet to reduced cardiovascular risk.

Circulation. 2008 Jan 15;117(2):169-75

**THE RELATIONSHIP BETWEEN ADHERENCE TO THE MEDITERRANEAN DIET AND THE SEVERITY AND SHORT-TERM PROGNOSIS OF ACUTE CORONARY SYNDROMES (ACS): THE GREEK STUDY OF ACS (THE GREECS).**

**BACKGROUND:** Although adherence to the Mediterranean diet has long been associated with lower incidence of various chronic diseases among apparently healthy individuals, its relationship with the severity and short prognosis (30 d) of patients with cardiovascular disease has rarely been investigated. **OBJECTIVE:** We sought to evaluate the association between adherence to the Mediterranean diet and the severity and prognosis of acute coronary syndromes. **METHODS:** From October 2003 to September 2004, a sample of 6 hospitals located in several urban and rural Greek regions was selected, and almost all survivors after an acute coronary syndrome were enrolled into the study (2,172 patients were included in the study; 76% were men and 24% women). Adherence to the Mediterranean diet was assessed by a diet score that incorporated the inherent characteristics of this diet. Higher values of the score (range 0-55) were closer to the Mediterranean diet. Biochemical indices of myocardial damage were also considered. **RESULTS:** Diet score was inversely correlated with entry values of cardiac troponin I ( $\rho = -0.19$ ,  $P < 0.001$ ), creatine phosphokinase ( $\rho = -0.09$ ,  $P < 0.001$ ), and creatine phosphokinase-MB ( $\rho = -0.09$ ,  $P < 0.001$ ). An increment in the diet score was associated with significant decrease in troponin I and creatine phosphokinase-MB levels ( $P < 0.01$ ) after adjusting for various potential confounders. Moreover, diet score was associated with lower risk of recurrent events (odds ratio = 0.81, 95% confidence interval 0.61-0.98). However, this association became insignificant when the discharge diagnosis of the patients was taken into account. **CONCLUSION:** Background dietary habits close to the Mediterranean diet seem to be associated with lower severity of coronary heart disease.

Nutrition. 2006 Jul-Aug;22(7-8):722-30

**MEDITERRANEAN DIETARY PATTERN AND PREDICTION OF ALL-CAUSE MORTALITY IN A US POPULATION: RESULTS FROM THE NIH-AARP DIET AND HEALTH STUDY.**

**BACKGROUND:** The Mediterranean diet has been suggested to play a beneficial role for health and longevity. However, to our knowledge, no prospective US study has investigated the Mediterranean dietary pattern in relation to mortality. **METHODS:** Study participants included 214,284 men and 166,012 women in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. During follow-up for all-cause mortality (1995-2005), 27,799

deaths were documented. In the first 5 years of follow-up, 5,985 cancer deaths and 3,451 cardiovascular disease (CVD) deaths were reported. We used a 9-point score to assess conformity with the Mediterranean dietary pattern (components included vegetables, legumes, fruits, nuts, whole grains, fish, monounsaturated fat-saturated fat ratio, alcohol, and meat). We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using age- and multivariate-adjusted Cox models. RESULTS: The Mediterranean diet was associated with reduced all-cause and cause-specific mortality. In men, the multivariate HRs comparing high to low conformity for all-cause, CVD, and cancer mortality were 0.79 (95% CI, 0.76-0.83), 0.78 (95% CI, 0.69-0.87), and 0.83 (95% CI, 0.76-0.91), respectively. In women, an inverse association was seen with high conformity with this pattern: decreased risks that ranged from 12% for cancer mortality to 20% for all-cause mortality ( $P = .04$  and  $P < .001$ , respectively, for the trend). When we restricted our analyses to never smokers, associations were virtually unchanged. CONCLUSION: These results provide strong evidence for a beneficial effect of higher conformity with the Mediterranean dietary pattern on risk of death from all causes, including deaths due to CVD and cancer, in a US population.

Arch Intern Med. 2007 Dec 10;167(22):2461-8

### **EFFECT OF A TRADITIONAL MEDITERRANEAN DIET ON LIPOPROTEIN OXIDATION: A RANDOMIZED CONTROLLED TRIAL.**

**BACKGROUND:** Despite the richness in antioxidants of the Mediterranean diet, to our knowledge, no randomized controlled trials have assessed its effect on in vivo lipoprotein oxidation. **METHODS:** A total of 372 subjects at high cardiovascular risk (210 women and 162 men; age range, 55-80 years), who were recruited into a large, multicenter, randomized, controlled, parallel-group clinical trial (the Prevención con Dieta Mediterránea [PREDIMED] Study) directed at testing the efficacy of the traditional Mediterranean diet (TMD) on the primary prevention of coronary heart disease, were assigned to a low-fat diet ( $n = 121$ ) or one of 2 TMDs (TMD + virgin olive oil or TMD + nuts). The TMD participants received nutritional education and either free virgin olive oil for all the family (1 L/wk) or free nuts (30 g/d). Diets were ad libitum. Changes in oxidative stress markers were evaluated at 3 months. **RESULTS:** After the 3-month interventions, mean (95% confidence intervals) oxidized low-density lipoprotein (LDL) levels decreased in the TMD + virgin olive oil (-10.6 U/L [-14.2 to -6.1]) and TMD + nuts (-7.3 U/L [-11.2 to -3.3]) groups, without changes in the low-fat diet group (-2.9 U/L [-7.3 to 1.5]). Change in oxidized LDL levels in the TMD + virgin olive oil group reached significance vs that of the low-fat group ( $P = .02$ ). Malondialdehyde changes in mononuclear cells paralleled those of oxidized LDL. No changes in serum glutathione peroxidase activity were observed. **CONCLUSIONS:** Individuals at high cardiovascular risk who improved their diet toward a TMD pattern showed significant reductions in cellular lipid levels and LDL oxidation. Results provide further evidence to recommend the TMD as a useful tool against risk factors for CHD.

Arch Intern Med. 2007 Jun 11;167(11):1195-203

### **A PILOT STUDY OF A MEDITERRANEAN-TYPE DIET INTERVENTION IN FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS LIVING IN AREAS OF SOCIAL DEPRIVATION IN GLASGOW.**

**BACKGROUND:** A Mediterranean-type diet rich in fish, fruit and vegetables and low in saturated fats has been associated with health benefits, including improved cardiovascular profile and benefit in RA. **OBJECTIVE:** To overcome obstacles to healthy eating by a community-based intervention promoting a Mediterranean-type diet in patients with RA living in socially deprived areas of Glasgow. **METHODS:** 130 female patients with RA aged 30-70 years (median 55), disease duration 8 years were recruited from three hospital sites. The intervention group ( $n = 75$ ) attended weekly 2-hour sessions for 6 weeks in the local community, including hands-on cooking classes backed up with written information. The control group ( $n = 55$ ) were given dietary written information only. Both groups completed food frequency questionnaires (FFQs), and clinical and laboratory measures were assessed at baseline, 3 and 6 months. **RESULTS:** Significant benefit was shown in the intervention group compared with controls for patient global assessment at 6 months ( $p = 0.002$ ), pain score at 3 and 6 months ( $p = 0.011$  and  $0.049$ ), early morning stiffness at 6 months ( $p = 0.041$ ) and Health Assessment Questionnaire score at 3 months ( $p = 0.03$ ). Analysis of the FFQs showed significant increases in weekly total fruit, vegetable and legume consumption and improvement in the ratio of monounsaturated:saturated fat intake and systolic BP in the intervention group only. The cooking classes were positively received by patients and tutors; cost/patient for the 6 week course was 84 pounds (124 euro). **CONCLUSIONS:** Results demonstrate that a 6 week intervention can improve consumption of healthier foods. If implemented more widely it may prove a popular, inexpensive and useful adjunct to other RA treatment.

Ann Rheum Dis. 2007 Sep;66(9):1239-43

### **THERE ARE MANY MEDITERRANEAN DIETS.**

Interest in Mediterranean diet began 30 years ago, when Ancel Keys published the results of the famous Seven Countries Study. Since 1945, almost 1.3 million people have come to Australia from Mediterranean countries as new settlers. There are 18 countries with coasts on the Mediterranean sea: Spain, southern France, Italy, Malta, Croatia, Bosnia, Albania, Greece, Cyprus, Turkey, Syria, Lebanon, Egypt, Libya, Malta, Tunisia, Algeria, and Morocco. This study from which this report derives aims to investigate the influence of the food habits of immigrants from Mediterranean countries on Australian food intake. Here we look at

the 'traditional' food habits of the above Mediterranean countries as told by 102 people we interviewed in Sydney, who came from 18 Mediterranean countries to Sydney. Most of the informants were women, their age ranged from 35 to 55 years. The interview was open-ended and held in the informant's home. It usually lasted around 1 1/2 hours. The interview had three parts. Personal information was obtained, questions relating to the food habits of these people back in their original Mediterranean countries and how their food intake and habits have changed in Australia were also asked. From the interviews, we have obtained a broad picture of 'traditional' food habits in different Mediterranean countries. The interview data was checked with books of recipes for the different countries. While there were similarities between the countries, there are also important differences in the food habits of the Mediterranean countries. Neighbouring countries' food habits are closer than those on opposite sides of the Mediterranean Sea. We suggest that these food habits can be put into four groups. The data here refer to food habits in Mediterranean countries 20 or 30 years ago, as they were recovering from the Second World War. There is no single ideal Mediterranean diet. Nutritionists who use the concept should qualify the individual country and the time in history of their model Mediterranean diet.

Asia Pac J Clin Nutr. 2001;10(1):2-9

### **ASSOCIATION OF DRINKING PATTERN AND ALCOHOL BEVERAGE TYPE WITH THE PREVALENCE OF METABOLIC SYNDROME, DIABETES, CORONARY HEART DISEASE, STROKE, AND PERIPHERAL ARTERIAL DISEASE IN A MEDITERRANEAN COHORT.**

The purpose of this study was to investigate the relationship between alcohol consumption and the prevalence of the metabolic syndrome (MetS), type 2 diabetes mellitus (DM), coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), and overall cardiovascular disease (CVD) in a Mediterranean cohort. It consisted of a cross-sectional analysis of a representative sample of Greek adults ( $n = 4,153$ ) classified as never, occasional, mild, moderate, or heavy drinkers. Cases with overt CHD, stroke, or PAD were recorded. In our population, 17% were never, 23% occasional, 27% mild, 24% moderate, and 9% heavy drinkers. Moderate alcohol consumption was associated with a lower trend for the prevalence of the MetS ( $P = .0001$ ), DM ( $P < .0001$ ), CHD ( $P = .0002$ ), PAD ( $P = .005$ ), and overall CVD ( $P = .001$ ) but not stroke compared with no alcohol use. Heavy drinking was associated with an increase in the prevalence of all of these disease states. Wine consumption was associated with a slightly better effect than beer or spirits consumption on the prevalence of total CVD, and beer consumption was associated with a better effect than spirits consumption. Alcohol intake was positively related with body weight, high-density lipoprotein cholesterol levels, and hypertension. Moderate alcohol consumption is associated with a lower prevalence of the MetS, DM, PAD, CHD, and overall CVD but not stroke compared with no alcohol use in a Mediterranean population. Heavy drinking was associated with an increase in the prevalence of all of these disease states. Advice on alcohol consumption should probably mainly aim at reducing heavy drinking.

Angiology. 2007 Dec-2008 Jan;58(6):689-97

### **THE ASSOCIATION BETWEEN ADHERENCE TO THE MEDITERRANEAN DIET AND FASTING INDICES OF GLUCOSE HOMOEOSTASIS: THE ATTICA STUDY.**

**OBJECTIVE:** We investigated the association between adherence to Mediterranean diet and fasting indices of glucose homeostasis, in a Greek adult population. **METHODS:** During 2001-2002 we randomly enrolled 1,514 men and 1,528 women (18-89 years old) without history of CVD, from the Attica area. Diabetes mellitus (type 2) and impaired fasting glucose (IFG) were defined according to the established ADA criteria. Insulin resistance was evaluated by HOMA-IR. Dietary habits were assessed through a validated food frequency questionnaire and a diet score (range 0-55) was developed (higher values means greater adherence to the Mediterranean diet). **RESULTS:** The overall prevalence of diabetes type 2 was 7.9% in men and 6.0% in women ( $P = 0.05$ ). Mean diet score was  $26.3 \pm 6.8$  in normoglycemic,  $25.7 \pm 6.4$  in IFG and  $22.2 \pm 5.8$  in diabetic subjects ( $p < 0.001$ ). In normoglycemic subjects who were in the upper tertile of the diet score we observed 7% lower glucose ( $p < 0.05$ ), 5% lower insulin ( $p < 0.05$ ) and 15% lower HOMA-IR ( $p < 0.01$ ) levels compared to subjects in the lower tertile of the diet score. Additionally, in diabetic/IFG participants who were in the upper tertile of the diet score we observed 15% lower glucose ( $p < 0.05$ ), 15% lower insulin ( $p < 0.05$ ) and 27% lower HOMA-IR ( $p < 0.01$ ) levels compared to those in the lower tertile. However, multiple regression analysis, adjusted for age, sex, BMI, waist-to-hip ratio, physical activity, smoking status, and presence of hypertension and hypercholesterolemia, confirmed the previous associations in normoglycemic, but not in diabetic/IFG people. **CONCLUSION:** An inverse association was observed between adherence to Mediterranean diet and indices of glucose homeostasis, only in normoglycemic people.

J Am Coll Nutr. 2007 Feb;26(1):32-8

### **ASSOCIATION BETWEEN THE PREVALENCE OF OBESITY AND ADHERENCE TO THE MEDITERRANEAN DIET: THE ATTICA STUDY.**

**OBJECTIVE:** We evaluated the prevalence of obesity in relation to adherence to a Mediterranean diet. **METHODS:** We conducted a cross-sectional survey that randomly enrolled 1,514 men (18 to 87 y old) and 1,528 women (18 to 89 y old) with no history of cardiovascular disease. Anthropometric indices were measured and frequency of various foods consumed during a usual week

was recorded. Adherence to a Mediterranean diet was assessed by a diet score that incorporated the inherent characteristics of this diet. RESULTS: Prevalences of overweight and obesity were 53% and 20% in men and 31% and 15% in women. An inverse relation was observed between diet score, waist-to-hip ratio ( $r = -0.31$ ,  $P < 0.001$ ), and body mass index ( $r = -0.4$ ,  $P < 0.001$ ) after adjusting for sex and age. Greater adherence to the Mediterranean diet (i.e., highest tertile) was associated with a 51% lower odds of being obese (odds ratio 0.49, 95% confidence interval 0.42 to 0.56) and a 59% lower odds of having central obesity (odds ratio 0.41, 95% confidence 0.35 to 0.47) compared with a non-Mediterranean diet (i.e., lowest tertile) after controlling for age, sex, physical activity status, metabolism, and other variables. CONCLUSION: We observed an inverse relation between adherence to a Mediterranean dietary pattern and prevalence of obesity in a free-eating, population-based sample of men and women, irrespective of various potential confounders.

Nutrition. 2006 May;22(5):449-56

### **MEDITERRANEAN DIET AND INSULIN SENSITIVITY, LIPID PROFILE AND BLOOD PRESSURE LEVELS, IN OVERWEIGHT AND OBESE PEOPLE; THE ATTICA STUDY.**

BACKGROUND: We aimed to investigate if overweight and obese adults "close" to Mediterranean diet present better insulin, lipids profile and better pressure levels, compared to individuals close to a more Westernized diet. METHODS: The ATTICA study is a population-based cohort that has randomly enrolled 3,042 adult men and women, stratified by age - gender, from the greater area of Athens, during 2001-2002. Of them, in this work we have studied 1,762 participants with excess body weight, meaning overweight (BMI: 25-29.9 kg/m<sup>2</sup>) and obese (BMI>30 kg/m<sup>2</sup>). 1,064 were men and 698 women (20-89 years old). Adherence to Mediterranean diet was assessed through a diet-score that was based on a validated food-frequency questionnaire. Blood pressure was measured and also fasting glucose, insulin and blood lipids. Insulin sensitivity was also assessed by the homeostasis model assessment (HOMA) approach (glucose x insulin/22.5). RESULTS: Individuals with excess bodyweight in the highest tertile of diet score, were more insulin sensitive than those in the lowest tertile (11.4% lower HOMA,  $p = 0.06$ ), had 13% lower levels of total cholesterol ( $p = 0.001$ ) and 3 mmHg decrease of systolic blood pressure levels ( $p < 0.001$ ), when adjusted for age, sex and BMI. Multivariate analysis after taking into account several confounders demonstrated that insulin sensitivity, total cholesterol and systolic blood pressure were independently but only modestly correlated with Mediterranean diet in people with excess bodyweight. CONCLUSION: Adherence to Mediterranean diet is modestly associated with a better insulin sensitivity, lower levels of total cholesterol and lower levels of systolic blood pressure in overweight and obese subjects. This may suggest that compared to general population, the beneficial effect of this diet in cardiovascular system of excess body weight people is limited.

Lipids Health Dis. 2007 Sep 19;6:22

### **MEDITERRANEAN DIET AND THE METABOLIC SYNDROME.**

The metabolic syndrome (also referred to as syndrome X or the insulin resistance syndrome) has emerged as an important cluster of risk factors for atherosclerotic disease. Patients with the syndrome also are at increased risk for developing type 2 diabetes mellitus. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia. Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome. Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity. Dietary patterns close to the Mediterranean diet and rich in fruit and vegetables, and high in monounsaturated fats are negatively associated with features of the metabolic syndrome. Some recent studies dealing specifically with the effect of interventions on the resolution of the metabolic syndrome have demonstrated a 25% net reduction in the prevalence of the syndrome following lifestyle changes mainly based on nutritional recommendations. Similar rates of resolution have been obtained with drugs, such as rosiglitazone and rimonabant. The favourable benefit/hazard ratio makes Mediterranean-style diets particularly promising to reduce the cardiovascular burden associated with the metabolic syndrome.

Mol Nutr Food Res. 2007 Oct;51(10):1268-74

### **MEDITERRANEAN DIET AND OSTEOPOROSIS PREVENTION.**

As a result of the demographic shift towards an ageing population, all industrialized countries face a growing prevalence of chronic age-related conditions, particularly osteoporosis. This multifaceted disease is defined as "a systemic skeletal disorder" characterized by low bone mass and micro-architectural deterioration of bone tissue, which results in increased bone fragility and susceptibility to fracture. Two main categories have been suggested: post-menopausal and senile osteoporosis. The prevention of osteoporosis through dietary means is especially challenging in technologically advanced societies. Indeed, within Europe, conspicuous differences are encountered in the severity of osteoporosis, the lowest incidence being reported in the Mediterranean area. The beneficial effect is attributed mainly to specific eating pattern. These food items contain a complex array of naturally occurring bioactive molecules with antioxidant, anti-inflammatory and alkalinising properties, that may contribute to the bone-sparing effect of Mediterranean diet.

## **MEDITERRANEAN DIET IN RELATION TO BODY MASS INDEX AND WAIST-TO-HIP RATIO.**

**OBJECTIVE:** The Mediterranean diet is rich in fat and starch, and hence may be related to overweight. We therefore investigated the relationship between adherence to a Mediterranean diet and body mass index (BMI) and waist-to-hip ratio (WHR). **DESIGN AND SETTING:** Data were obtained from the control group of a network of case-control studies on cancer conducted in major teaching and general hospitals in four Italian areas between 1991 and 2002. An interviewer-administered validated 78-item food-frequency questionnaire was used to obtain information on the subjects' habitual diet. Information on socio-economic factors, lifestyle habits and anthropometric measures was also collected. A Mediterranean diet score (MDS) was derived on the basis of eight characteristics of the Mediterranean diet. **SUBJECTS:** Subjects were 6,619 patients (3,090 men, 3,529 women) admitted to hospital for a wide spectrum of acute, non-neoplastic conditions, unrelated to known risk factors for cancer and long-term modifications of diet. **RESULTS:** In multiple linear regression models adjusted for age, study centre, education, tobacco smoking, occupational physical activity and total energy intake, the MDS was not related to BMI (beta = 0.05 for men and -0.04 for women) or WHR (beta = 0.000 and 0.001, respectively) in both sexes. **CONCLUSIONS:** Adherence to the major characteristics of the Mediterranean diet is unrelated to BMI and WHR, confirming previous data from Greece and Spain.

Public Health Nutr. 2008 Feb;11(2):214-7

## Ribose

### **CATALYTIC AND MECHANICAL CYCLES IN F-ATP SYNTHASES. FOURTH IN THE CYCLES REVIEW SERIES.**

Cycles have a profound role in cellular life at all levels of organization. Well-known cycles in cell metabolism include the tricarboxylic acid and the urea cycle, in which a specific carrier substrate undergoes a sequence of chemical transformations and is regenerated at the end. Other examples include the interconversions of cofactors, such as NADH or ATP, which are present in the cell in limiting amounts and have to be recycled effectively for metabolism to continue. Every living cell performs a rapid turnover of ATP to ADP to fulfil various energetic demands and effectively regenerates the ATP from ADP in an energy-consuming process. The turnover of the ATP cycle is impressive; a human uses about its body weight in ATP per day. Enzymes perform catalytic reaction cycles in which they undergo several chemical and physical transformations before they are converted back to their original states. The ubiquitous F<sub>1</sub>F<sub>0</sub> ATP synthase is of particular interest not only because of its biological importance, but also owing to its unique rotational mechanism. Here, we give an overview of the membrane-embedded F<sub>0</sub> sector, particularly with respect to the recent crystal structure of the c ring from *Ilyobacter tartaricus*, and summarize current hypotheses for the mechanism by which rotation of the c ring is generated.

EMBO Rep. 2006 Mar;7(3):276-82

### **RIBOSE ACCELERATES THE REPLETION OF THE ATP POOL DURING RECOVERY FROM REVERSIBLE ISCHEMIA OF THE RAT MYOCARDIUM.**

It is a characteristic feature of the myocardium that the derangement in function [6] and the depletion of the ATP pool [1, 2, 9] that occur subsequent to oxygen deficiency persist when blood flow is restored. Of renewed interest is the inability of the heart to replenish rapidly its adenine nucleotide pool once it has been diminished during a brief period of regional ischemia [2, 9]. A hypothesis that could explain this metabolic insufficiency of the myocardium is that the biosynthesis of adenine nucleotides is very slow in the normal heart and is increased only moderately during postischemic recovery [15] so that the replenishment of adenine nucleotides is not affected appreciably. To substantiate such a hypothesis it is necessary to provide evidence that the restitution of the ATP pool can be accelerated by stimulation of this biosynthetic process. In previous studies ribose has been recognized as a substrate that enhances markedly adenine nucleotide biosynthesis in the rat heart [11, 12]. We now demonstrate that continuous i.v. infusion of ribose during recovery from a 15-min period of myocardial ischemia in rats leads to restoration of the cardiac ATP pool within 12 h, whereas 72 h are needed for ATP normalization without any intervention.

J Mol Cell Cardiol. 1984 Sep;16(9):863-6

### **INFLUENCE OF RIBOSE ON ADENINE SALVAGE AFTER INTENSE MUSCLE CONTRACTIONS.**

The influence of ribose supplementation on skeletal muscle adenine salvage rates during recovery from intense contractions and subsequent muscle performance was evaluated using an adult rat perfused hindquarter preparation. Three minutes of tetanic contractions (60 tetani/min) decreased ATP content in the calf muscles by approximately 50% and produced an equimolar increase in IMP. Effective recovery of muscle ATP 1 h after contractions was due to reamination of IMP via the purine nucleotide cycle and was complete in the red gastrocnemius but incomplete in the white gastrocnemius muscle section. Adenine salvage rates in recovering muscle averaged 45 +/- 4, 49 +/- 5, and 30 +/- 3 nmol. h<sup>-1</sup>. g<sup>-1</sup> for plantaris, red gastrocnemius, and white gastrocnemius muscle, respectively, which were not different from values in corresponding nonstimulated muscle sections. Adenine salvage rates increased five- to sevenfold by perfusion with approximately 4 mM ribose (212 +/- 17, 192 +/- 9, and 215 +/- 14 nmol. h<sup>-1</sup>. g<sup>-1</sup> in resting muscle sections, respectively). These high rates were sustained in recovering muscle, except for a small (approximately 20%) but significant (P < 0.001) decrease in the white gastrocnemius muscle. Ribose supplementation did not affect subsequent muscle force production after 60 min of recovery. These data indicate that adenine salvage rates were essentially unaltered during recovery from intense contractions.

J Appl Physiol. 2001 Oct;91(4):1775-81

### **EFFECT OF RIBOSE SUPPLEMENTATION ON RESYNTHESIS OF ADENINE NUCLEOTIDES AFTER INTENSE INTERMITTENT TRAINING IN HUMANS.**

The effect of oral ribose supplementation on the resynthesis of adenine nucleotides and performance after 1 wk of intense

intermittent exercise was examined. Eight subjects performed a random double-blind crossover design. The subjects performed cycle training consisting of 15 x 10 s of all-out sprinting twice per day for 7 days. After training the subjects received either ribose (200 mg/kg body wt; Rib) or placebo (Pla) three times per day for 3 days. An exercise test was performed at 72 h after the last training session. Immediately after the last training session, muscle ATP was lowered ( $P < 0.05$ ) by 25 +/- 2 and 22 +/- 3% in Pla and Rib, respectively. In both Pla and Rib, muscle ATP levels at 5 and 24 h after the exercise were still lower ( $P < 0.05$ ) than pretraining. After 72 h, muscle ATP was similar ( $P > 0.05$ ) to pretraining in Rib (24.6 +/- 0.6 vs. 26.2 +/- 0.2 mmol/kg dry wt) but still lower ( $P < 0.05$ ) in Pla (21.1 +/- 0.5 vs. 26.0 +/- 0.2 mmol/kg dry wt) and higher ( $P < 0.05$ ) in Rib than in Pla. Plasma hypoxanthine levels after the test performed at 72 h were higher ( $P < 0.05$ ) in Rib compared with Pla. Mean and peak power outputs during the test performed at 72 h were similar ( $P > 0.05$ ) in Pla and Rib. The results support the hypothesis that the availability of ribose in the muscle is a limiting factor for the rate of resynthesis of ATP. Furthermore, the reduction in muscle ATP observed after intense training does not appear to be limiting for high-intensity exercise performance.

Am J Physiol Regul Integr Comp Physiol. 2004 Jan;286(1):R182-8

### **D-RIBOSE IMPROVES DIASTOLIC FUNCTION AND QUALITY OF LIFE IN CONGESTIVE HEART FAILURE PATIENTS: A PROSPECTIVE FEASIBILITY STUDY.**

Patients with chronic coronary heart disease often suffer from congestive heart failure (CHF) despite multiple drug therapies. D-Ribose has been shown in animal models to improve cardiac energy metabolism and function following ischaemia. This was a prospective, double blind, randomized, crossover design study, to assess the effect of oral D-ribose supplementation on cardiac hemodynamics and quality of life in 15 patients with chronic coronary artery disease and CHF. The study consisted of two treatment periods of 3 weeks, during which either oral D-ribose or placebo was administered followed by a 1-week wash out period, and then administration of the other supplement. Assessment of myocardial functional parameters by echocardiography, quality of life using the SF-36 questionnaire and functional capacity using cycle ergometer testing was performed. The administration of D-ribose resulted in an enhancement of atrial contribution to left ventricular filling (40+/-11 vs. 45+/-9%,  $P=0.02$ ), a smaller left atrial dimension (54+/-20 vs. 47+/-18 ml,  $P=0.02$ ) and a shortened E wave deceleration (235+/-64 vs. 196+/-42,  $P=0.002$ ) by echocardiography. Further, D-ribose also demonstrated a significant improvement of the patient's quality of life (417+/-118 vs. 467+/-128,  $P < 0.01$ ). In comparison, placebo did not result in any significant echocardiographic changes or in quality of life. This feasibility study in patients with coronary artery disease in CHF revealed the beneficial effects of D-ribose by improving diastolic functional parameters and enhancing quality of life.

Eur J Heart Fail. 2003 Oct;5(5):615-9

### **D-RIBOSE AS A SUPPLEMENT FOR CARDIAC ENERGY METABOLISM.**

Metabolic support for the heart has been an attractive concept since the pioneering work of Sodi-Pallares et al. four decades ago.\* Recently, interest has increased in the use of over-the-counter supplements and naturally occurring nutraceuticals for enhancement of cardiac and skeletal muscle performance. These include amino acids such as creatine, L-carnitine, and L-arginine, as well as vitamins and cofactors such as alpha-tocopherol and coenzyme Q. Like these other molecules, D-ribose is a naturally occurring compound. It is the sugar moiety of ATP and has also received interest as a metabolic supplement for the heart. The general hypothesis is that under certain pathologic cardiac conditions, nucleotides (particularly ATP, ADP, and AMP) are degraded and lost from the heart. The heart's ability to resynthesize ATP is then limited by the supply of D-ribose, which is a necessary component of the adenine nucleotide structure. In support of this hypothesis, recent reports have used D-ribose to increase tolerance to myocardial ischemia. Its use in patients with stable coronary artery disease improves time to exercise-induced angina and electrocardiographic changes. In conjunction with thallium imaging or dobutamine stress echocardiography, D-ribose supplementation has been used to enhance detection of hibernating myocardium. In this article, we review the biochemical basis for using supplemental D-ribose as metabolic support for the heart and discuss the experimental evidence for its benefit.

J Cardiovasc Pharmacol Ther. 2000 Oct;5(4):249-58

### **ISCHEMIC HEART DISEASE: METABOLIC APPROACHES TO MANAGEMENT.**

The number of patients with coronary artery disease and its risk factors is increasing in Western nations. New treatments for these patients may soon include a class of agents known as the metabolic modulators. This group of agents consists of the partial fatty acid oxidation inhibitors trimetazidine and ranolazine, as well as dichloroacetate, which promotes carbohydrate utilization. Metabolic modulators also include the nutraceuticals L-carnitine and D-ribose. The available evidence regarding the benefits of each of these five agents is reviewed.

Clin Cardiol. 2004 Aug;27(8):439-41

### **EFFECTS OF RIBOSE ON EXERCISE-INDUCED ISCHAEMIA IN STABLE CORONARY ARTERY DISEASE.**

There is no established treatment specifically aimed at protecting or restoring cardiac energy metabolism, which is greatly impaired by ischaemia. Even after reperfusion, myocardial content of ATP remains low for more than 72 h. Long-term post-ischaemic dysfunction and irreversibility of ischaemic damage have been associated with low ATP content. Evidence that the pentose sugar ribose stimulates ATP synthesis and improves cardiac function led us to test the possibility that ribose increases tolerance to myocardial ischaemia in patients with coronary artery disease (CAD). 20 men with documented severe CAD underwent two symptom-limited treadmill exercise tests on 2 consecutive days; we postulated that the ischaemia induced might bring about changes in ATP metabolism lasting for several days. Patients whose baseline tests showed reproducibility were randomly allocated 3 days of treatment with placebo or ribose 60 g daily in four doses by mouth. Exercise testing was repeated after treatment on day 5. At that time mean (95% confidence interval) treadmill walking time until 1 mm ST-segment depression was significantly greater in the ribose than in the placebo group (276 [220-331] vs 223 [188-259] s;  $p = 0.002$ ). The groups did not differ significantly in time to moderate angina. In the ribose-treated group the changes from baseline to day 5 in both time to ST depression and time to moderate angina were significant ( $p$  less than 0.005), but these changes were not significant in the placebo group. In patients with CAD, administration of ribose by mouth for 3 days improved the heart's tolerance to ischaemia. The presumed effects on cardiac energy metabolism offer new possibilities for adjunctive medical treatment of myocardial ischaemia.

Lancet. 1992 Aug 29;340(8818):507-10

### **THE BENEFITS OF RIBOSE IN CARDIOVASCULAR DISEASE.**

Cardiovascular disease still ranks as the leading cause of death in men and women. Adults have tried to lower their risk of cardiovascular disease by improving their diet, quitting smoking, controlling blood pressure and exercising regularly. Additionally, many adults have turned to nutraceutical or natural products. Myocardial ischemia, produces a depression in myocardial tissue levels of high energy compounds, along with a compromise in myocardial function. Ribose, a naturally occurring sugar, has been extensively investigated, both in animal and clinical studies, as an agent to enhance the recovery of these depressed energy compounds. Results of these studies have been promising in enhancing the recovery of these energy molecules along with an improvement in myocardial function. Therefore, ribose should be considered as a potential agent in the treatment of ischemic cardiovascular disease.

Med Hypotheses. 2003 Feb;60(2):149-51

### **RIBOSE INFUSION ACCELERATES THALLIUM REDISTRIBUTION WITH EARLY IMAGING COMPARED WITH LATE 24-HOUR IMAGING WITHOUT RIBOSE.**

To determine if early (4-h) thallium-201 imaging with ribose infusion would enhance detection of thallium redistribution better than late (24-h) imaging without ribose infusion, 15 patients with coronary artery disease underwent thallium stress tests by both methods within 2 weeks. All 15 patients had quantitative coronary angiography. After immediate postexercise planar imaging during the first of two exercise tests, patients were randomized to receive either intravenous ribose (3.3 mg/kg per min) or a control infusion of saline solution for 30 min. Images performed at 4 h for the ribose study were compared with those at 24 h for the saline control study. During the second test, exercise was carried to the same rate-pressure product and each patient received the opposite infusion. Four-hour postexercise images after ribose infusion identified 21 reversible defects not seen in the 24-h saline study. Three reversible defects were seen only in saline studies, but not with ribose at 4 h ( $p$  less than 0.01); 15 reversible defects were seen with both tests. When analyzed with respect to the 31 vascular territories supplied by a coronary artery with a greater than 50% stenosis, 8 territories had reversible defects present in the ribose but not the saline study and the saline study did not demonstrate reversible defects in territories that were seen in the ribose study ( $p$  less than 0.01). In 14 of these territories, reversible defects were seen with both tests. In 6 of 15 patients, additional vascular territories with reversible defects were identified after ribose infusion. It is concluded that ribose enhances the detection of thallium redistribution at 4 h compared with 24-h control images in patients with coronary artery disease and, therefore, substantially improves the identification of viable ischemic myocardium.

J Am Coll Cardiol. 1991 Dec;18(7):1671-81

### **RIBOSE FACILITATES THALLIUM-201 REDISTRIBUTION IN PATIENTS WITH CORONARY ARTERY DISEASE.**

To investigate whether i.v. infusion of ribose, an adenine nucleotide precursor, postischemia facilitates thallium-201 (201Tl) redistribution and improves identification of ischemic myocardium in patients with coronary artery disease (CAD), 17 patients underwent two exercise 201Tl stress tests, performed 1-2 wk apart. After immediate postexercise planar imaging, patients received either i.v. ribose (3.3 mg/kg/min x 30 min) or saline as a control. Additional imaging was performed 1 and 4 hr postexercise. Reversible defects were identified by count-profile analysis. Significantly more (nearly twice as many) reversible 201Tl defects were identified on the post-ribose images compared to the post-saline (control) images at both 1 and 4 hr postexercise ( $p$  less than 0.001). Quantitative analyses of the coronary arteriogram was available in 13 patients and confirmed

that the additional reversible defects were in myocardial regions supplied by stenosed arteries. We conclude that ribose appears to facilitate 201TI redistribution in patients with CAD and enhances identification of ischemic myocardium.

J Nucl Med. 1991 Feb;32(2):193-200

### **EFFECTS OF RIBOSE SUPPLEMENTATION ON REPEATED SPRINT PERFORMANCE IN MEN.**

This study used a randomized, placebo-controlled, crossover design to evaluate the effects of oral ribose supplementation on short-term anaerobic performance. After familiarization, subjects performed 2 bouts of repeated cycle sprint exercise (six 10-second sprints with 60-second rest periods between sprints) in a single day. After the second exercise, subjects ingested 32 g of ribose or cellulose (4 x 8-g doses) during the next 36 hours. After supplementation, subjects returned to the laboratory to perform a single bout of cycle sprinting (as described above). After a 5-day washout period, subjects repeated the protocol, receiving the opposite supplement treatment. Ribose supplementation led to statistically significant increases in mean power and peak power in sprint 2 (10.9 and 6.6%, respectively) and higher (although not significant) absolute values in sprints 1, 3, and 4. In conclusion, ribose supplementation did not show reproducible increases in performance across all 6 sprints. Therefore, within the framework of this investigation, it appears that ribose supplementation does not have a consistent or substantial effect on anaerobic cycle sprinting.

J Strength Cond Res. 2003 Feb;17(1):47-52

### **RIBOSE VERSUS DEXTROSE SUPPLEMENTATION, ASSOCIATION WITH ROWING PERFORMANCE: A DOUBLE-BLIND STUDY.**

**OBJECTIVE:** It has been hypothesized that ribose supplementation rapidly replenishes adenosine triphosphate stores and thereby improves exercise performance. We compared the effects of ribose versus dextrose on rowing performance. **DESIGN:** Double-blind randomized trial. **SETTING:** Rowing team training area of large midwestern university. **PARTICIPANTS:** Thirty-one women collegiate rowers. **INTERVENTIONS:** We studied the effects of ribose versus dextrose supplementation (10 g each in 8 oz water) for 8 weeks before and after practice and 2000-m time trials. **OUTCOME MEASUREMENTS AND RESULTS:** In the time trials, the dextrose group showed significantly more improvement at 8 weeks than the ribose group (median, 15.2 vs. 5.2 s;  $P = 0.031$ ). **CONCLUSIONS:** We doubt ribose impaired, and hypothesize dextrose enhanced, rowing performance. Further research is needed to define what role, if any, dextrose and ribose play as athletic supplements.

Clin J Sport Med. 2006 Jan;16(1):68-71

## Bromelain

### **BROMELAIN AS A TREATMENT FOR OSTEOARTHRITIS: A REVIEW OF CLINICAL STUDIES.**

Bromelain, an extract from the pineapple plant, has been demonstrated to show anti-inflammatory and analgesic properties and may provide a safer alternative or adjunctive treatment for osteoarthritis. All previous trials, which have been uncontrolled or comparative studies, indicate its potential use for the treatment of osteoarthritis. This paper reviews the mechanism of its putative therapeutic actions, those clinical trials that have assessed its use in osteoarthritis to date, as well as considering the safety implications of this supplement for osteoarthritis and reviewing the evidence to date regarding the dosage for treating this condition. The data available at present indicate the need for trials to establish the efficacy and optimum dosage for bromelain and the need for adequate prospective adverse event monitoring in such chronic conditions as osteoarthritis.

Evid Based Complement Alternat Med. 2004 Dec;1(3):251-257

### **EFFICACY AND TOLERANCE OF AN ORAL ENZYME COMBINATION IN PAINFUL OSTEOARTHRITIS OF THE HIP. A DOUBLE-BLIND, RANDOMISED STUDY COMPARING ORAL ENZYMES WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.**

**OBJECTIVE:** The objective of this study was to establish the non-inferiority of an oral enzyme therapy (Phlogenzym-(PE)) as compared to the non-steroidal anti-inflammatory drug (NSAID) diclofenac (DC) in patients with osteoarthritis (OA) of the hip. **METHODS:** Ninety patients presenting with painful episodes of OA of the hip were treated for 6 weeks in one study centre in a phase III, randomised, double blind, parallel group trial. Altogether, 45 patients were treated in the PE group and 45 patients were treated in the DC group. Primary efficacy criteria were: WOMAC dimensions pain, joint stiffness and function, and Lequesne index as multiple endpoint according to O'Brien. The efficacy criteria were analysed applying the test of non-inferiority with regard to mean changes and frequencies, t-test, U test, ANCOVA and descriptive methods. **RESULTS:** Within the 6 weeks observation period, the adjusted changes from baseline to endpoint of the target parameters worked out as follows (adjusted differences, mean +/- SEM): WOMAC subscale pain (PE -10.3 +/- 1.2, DC -9.5 +/- 1.2), WOMAC subscale joint stiffness (PE -3.9 +/- 0.5, DC -3.6 +/- 0.5), WOMAC subscale physical function (PE -31.7 +/- 3.5, DC -29.7 +/- 3.5), Lequesne's index (PE -2.89 +/- 0.47, DC -2.27 +/- 0.47). Non-inferiority of PE as compared to DC with regard to the O'Brien's global sum of the standardised adjusted changes from baseline to endpoint in pain, stiffness, physical function, and Lequesne's index was established with  $p = 0.0025$ . PE was simultaneously non-inferior as compared to DC with regard to the 4 single endpoints: WOMAC subscale pain ( $p = 0.0033$ ), WOMAC subscale joint stiffness ( $p = 0.0061$ ), WOMAC subscale physical function ( $p = 0.0039$ ), Lequesne's index ( $p = 0.0008$ ) (closed test procedure). The equivalence tests remained insignificant due to comparatively lower effects of DC. For 71.1% of the PE patients and for 61.4% of the DC patients rates of good or very good global investigator assessments of efficacy were calculated (test of non-inferiority:  $p = 0.0011$ ). In the majority of patients, tolerability was judged in both drug groups as very good or good. **CONCLUSION:** This trial showed significant non-inferiority from 6 weeks treatment with PE in patients with OA of the hip with regard to the WOMAC dimensions pain, stiffness and physical function, to Lequesne's index, to the investigator and patients assessments of efficacy, and to the responder rates based on pain, physical function, and patient assessment of efficacy. With regard to drug tolerability some tendencies in favour of PE were detected. However, in this study there was no real difference between PE and DC 100 mg/day, implying an equal benefit-risk relation between the substances. PE may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level.

Clin Exp Rheumatol. 2006 Jan-Feb;24(1):25-30

### **ORAL ENZYME COMBINATION VERSUS DICLOFENAC IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE--A DOUBLE-BLIND PROSPECTIVE RANDOMIZED STUDY.**

The aim of this study was to compare the efficacy and safety of an oral enzyme-rutosid combination (ERC) containing rutosid and the enzymes bromelain and trypsin, with that of diclofenac in patients with osteoarthritis (OA) of the knee. A total of 103 patients presenting with painful episodes of OA of the knee were treated for 6 weeks in two study centers in a randomized, double-blind, parallel group trial. Altogether, 52 patients were treated in the ERC group and 51 patients were treated in the diclofenac group. Primary efficacy criteria were Lequesne's Algofunctional Index (LFI) and a 'complaint index', including pain at rest, pain on motion and restricted function. The efficacy criteria were analyzed by applying the Wilcoxon-Mann-Whitney test that provides the Mann-Whitney estimator (MW) as a measure of relevance. Non-inferiority was considered to be proven if the lower

bound of the 97.5% one-sided confidence interval (CI-LB) was higher than MW = 0.36 (benchmark of not yet relevant inferiority). Both treatments resulted in clear improvements. Within the 6-week observation period, the mean value of the LFI decreased from 13.0 to 9.4 in the ERC group and from 12.5 to 9.4 in the diclofenac group. Non-inferiority of ERC was demonstrated by both primary criteria, LFI (MW = 0.5305; CI-LB = 0.4171) and complaint index (MW = 0.5434; CI-LB = 0.4296). Considerable improvements were also seen in secondary efficacy criteria, with a slight tendency towards superiority of ERC. The global judgment of efficacy by physician resulted in at least good ratings for 51.4% of the ERC patients, and for 37.2% of the diclofenac patients. In the majority of patients tolerability was judged in both drug groups as very good or good. The current study indicates that ERC can be considered as an effective and safe alternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee. Placebo-controlled studies are now needed to confirm these results.

Clin Rheumatol. 2004 Oct;23(5):410-5

### **A DOUBLE BLIND, RANDOMISED, PARALLEL GROUP STUDY ON THE EFFICACY AND SAFETY OF TREATING ACUTE LATERAL ANKLE SPRAIN WITH ORAL HYDROLYTIC ENZYMES.**

**OBJECTIVE:** To compare the effectiveness and safety of the triple combination Phlogenzym (rutoside, bromelain, and trypsin) with double combinations, the single substances, and placebo. **DESIGN:** Multinational, multicentre, double blind, randomised, parallel group design with eight groups structured according to a factorial design. **SETTING:** Orthopaedic surgery and emergency departments in 27 European hospitals. **PARTICIPANTS:** A total of 721 patients aged 16-53 years presenting with acute unilateral sprain of the lateral ankle joint. **PRIMARY EFFICACY CRITERIA:** (a) Pain on walking one or two steps, as defined by the patient on a visual analogue scale. (b) The range of motion, as measured by the investigator and expressed as a sum of flexion and extension. (c) The volume of the injured ankle measured with a volometer. **RESULTS:** At the primary end point at seven days, the greatest reduction in pain was in the bromelain/trypsin group (73.7%). The Phlogenzym group showed a median reduction of 60.3%, and the placebo group showed a median reduction of 73.3%. The largest increase in range of motion (median) was in the placebo group (60% change from baseline). The Phlogenzym group showed a median increase of 42.9%. The biggest decrease in swelling was in the trypsin group (3.9% change from baseline). The Phlogenzym group showed a -2.30% change from baseline and the placebo group a -2.90% change. In the subgroup analysis of patients who did not use a Caligamed brace, Phlogenzym was superior to placebo for the summarising directional test of the primary efficacy criteria (MW = 0.621; LB-CI 0.496;  $p = 0.029$ ; one sided Wei-Lachin procedure). The vast majority of doctors and patients rated the tolerability of all treatments tested as very good or at least good. **CONCLUSIONS:** Phlogenzym was not found to be superior to the three two-drug combinations, the three single substances, or placebo for treatment of patients with acute unilateral sprain of the lateral ankle joint. The small subgroup of patients treated without the support of a Caligamed brace showed evidence of superiority of Phlogenzym over placebo. Further research is warranted to study this effect of Phlogenzym in patients treated without ankle support.

Br J Sports Med. 2004 Aug;38(4):431-5

### **SYSTEMIC ENZYME THERAPY IN THE TREATMENT AND PREVENTION OF POST-TRAUMATIC AND POSTOPERATIVE SWELLING.**

**PURPOSE OF THE STUDY:** The authors concentrate on the use of enzyme therapy in traumatology. They monitored SET efficiency in the treatment and prophylaxis of swelling in the postoperative period after the internal fixation of fractures of long bones and compared it with the effect of standard antioedematous drugs on the basis of aescin. **MATERIAL:** A group of 60 patients was followed after the fixation of long bones. The average age was 42 years (range, 12-79 years). Fractures were treated by intramedullary fixation or by external fixators. The patients were split into two groups. In 30 patients only Phlogenzym was administered for the treatment and prevention of posttraumatic and postoperative swelling. Another 30 patients--the control group--were treated by standard antioedematous drugs on the basis of aescin. The same analgesics were applied in both groups. **METHODS:** The group of patients with systemic enzyme therapy were treated by Phlogenzym in the dosage 3 times 3 tablets in the first three days after operation and subsequently 3 times 2 tablets in the remaining follow-up period. In the postoperative period the changes of operated limb volume was monitored. The circumference of a limb was measured in the area of the largest oedema and 10 cm distally. Then the volume of this part of limb was calculated as the volume of conical frustum. The measurements were performed on postoperative days 1, 3, 5, 7, 10 and 14. The volume value of the 1st day was used as starting value (100%). The values of subsequent measurements were then compared to this starting value in both group of patients. Evaluation of the resorption of traumatic and postoperative haematoma and analgesic effect of Phlogenzym was also made. **RESULTS:** In the group of patients who were administered with Phlogenzym after operation the reduction of the posttraumatic and postoperative swelling was continuous and significantly faster in compared with patients of the control group. A remarkable difference was revealed by the measurement on 5th postoperative day--in patients treated by Phlogenzym the starting value of the volume of the operated limb was reduced on average by almost 8%. In contrast, in the control group treated by standard drugs this value slightly increased above 100%. At the end of the first postoperative week the monitored volume was on average reduced by 12% in the SET group compared with 1.45% in the control group. At the end of the follow-up--on 14th postoperative day the volume was reduced in the SET group by almost 17% compared with 9% in the control group. There was also an evidently good analgesic effect of the drug. The total consumption of analgesics of patients in the SET group was significantly lower, particularly in the early postoperative period. In the course of the follow-up of both groups no marked differences were recorded in the changes of the volume of operated limbs in dependence on the method of fixation applied

(intramedullary or external), sex of the patient or on the affected limb (lower or upper). The patients tolerated Phlogenzym very well, only one female patient suffered temporarily from poor digestion which, however, did not require to interrupt the administration of the drug. No other undesirable effects occurred. DISCUSSION: Fixation of long bones belongs to the most frequent operations in traumatological and orthopaedic departments of all levels. One of the factors which may have an unfavourable effect on the final result of fixation is a prolonged post-trauma or postoperative swelling. The results of the study prove a clearly positive effect of system enzymotherapy on the reduction of oedema accompanying the trauma and inflammation. The study proved a statistical significance of the acceleration of the reduction of oedema in patients treated by Phlogenzym as compared to the control group treated by a standard antioedematous drugs. CONCLUSION: The authors verified that systemic enzyme therapy could influence significantly the results of traumatological surgery. Simple administration per os, efficient oedema reduction and thus accelerated healing, antiophlogistic and analgesic effect--all these advantages justify the application of this therapeutic method what can be recommended as a part of the complex treatment in traumatology with both conservative and surgical approaches.

Acta Chir Orthop Traumatol Cech. 2001;68(1):45-9

### **THERAPEUTIC USE, EFFICIENCY AND SAFETY OF THE PROTEOLYTIC PINEAPPLE ENZYME BROMELAIN-POS IN CHILDREN WITH ACUTE SINUSITIS IN GERMANY.**

The therapeutic efficiency and safety of the proteolytic enzyme bromelaine obtained from pineapple (Bromelain-POS, Ursapharm GmbH, Saarbrücken, Germany) was evaluated in children under the age of 11 years diagnosed with acute sinusitis. Data from 116 patients from 19 centres located across Germany were analysed in a pharmacoepidemiological cohort study. Patient cohorts were either treated with Bromelain-POS (N = 62), in combination with Bromelain-POS and standard therapies (N = 34), or with standard therapies (N = 20). The primary parameter measuring effectiveness of the different treatment groups was the duration of symptoms. The shortest mean period of symptoms was observed in patients treated with Bromelain-POS alone (6.66 days), followed by the standard therapy (7.95 days) and those treated with a combination of Bromelain-POS and the standard therapy (9.06 days). Patients of the Bromelain-POS monotherapy group showed a statistically significant faster recovery from symptoms ( $p = 0.005$ ) compared to the other treatment groups. One 10-year-old male patient, with a known pineapple allergy, showed a self-limiting mild allergic reaction. No other unwanted side-effects were reported. This trial documents that the proteolytic pineapple enzyme Bromelain-POS is widely used in the treatment of young children diagnosed with acute sinusitis in Germany and that the use of proteolytic enzymes can benefit such patients.

In Vivo. 2005 Mar-Apr;19(2):417-21

### **IN VIVO ANTITUMORAL ACTIVITY OF STEM PINEAPPLE (ANANAS COMOSUS) BROMELAIN.**

Stem bromelain (EC 3.4.22.32) is a major cysteine proteinase, isolated from pineapple (Ananas comosus) stem. Its main medicinal use is recognized as digestive, in vaccine formulation, antitumoral and skin debrider for the treatment of burns. To verify the identity of the principle in stem fractions responsible for the antitumoral effect, we isolated bromelain to probe its pharmacological effects. The isolated bromelain was obtained from stems of adult pineapple plants by buffered aqueous extraction and cationic chromatography. The homogeneity of bromelain was confirmed by reverse phase HPLC, SDS-PAGE and N-terminal sequencing. The in vivo antitumoral/antileukemic activity was evaluated using the following panel of tumor lines: P-388 leukemia, sarcoma (S-37), Ehrlich ascitic tumor (EAT), Lewis lung carcinoma (LLC), MB-F10 melanoma and ADC-755 mammary adenocarcinoma. Intraperitoneal administration of bromelain (1, 12.5, 25 mg/kg), began 24 h after tumor cell inoculation in experiments in which 5-fluorouracil (5-FU, 20 mg/kg) was used as positive control. The antitumoral activity was assessed by the survival increase (% survival index) following various treatments. With the exception of MB-F10 melanoma, all other tumor-bearing animals had a significantly increased survival index after bromelain treatment. The largest increase (approximately 318 %) was attained in mice bearing EAT ascites and receiving 12.5 mg/kg of bromelain. This antitumoral effect was superior to that of 5-FU, whose survival index was approximately 263 %, relative to the untreated control. Bromelain significantly reduced the number of lung metastasis induced by LLC transplantation, as observed with 5-FU. The antitumoral activity of bromelain against S-37 and EAT, which are tumor models sensitive to immune system mediators, and the unchanged tumor progression in the metastatic model suggests that the antimetastatic action results from a mechanism independent of the primary antitumoral effect.

Planta Med. 2007 Oct;73(13):1377-83

### **BROMELAIN REDUCES MILD ACUTE KNEE PAIN AND IMPROVES WELL-BEING IN A DOSE-DEPENDENT FASHION IN AN OPEN STUDY OF OTHERWISE HEALTHY ADULTS.**

There is preliminary clinical evidence to support the contention that the anti-inflammatory and analgesic properties of bromelain help to reduce symptoms of osteo- and rheumatoid arthritis. However, there have been no controlled studies of its effects on joint health in healthy subjects who lack such diagnosis. The current study investigated the effects of bromelain on mild acute knee pain of less than 3 months duration in otherwise healthy adults. The study was an open, dose-ranging postal study in volunteers who had been recruited through newspaper and magazine articles. Two validated questionnaires (WOMAC knee health Index and

the Psychological Well-Being Index) were completed at baseline and after one month's intervention with bromelain, randomly allocated to volunteers as either 200 mg or 400 mg per day. Seventy seven subjects completed the study. In both treatment groups, all WOMAC symptom dimension scores were significantly reduced compared with baseline, with reductions in the final battery (total symptom score) of 41 and 59% ( $P = 0.0001$  and  $<0.0001$ ) in the low and high dose groups respectively. In addition, improvements in total symptom score ( $P = 0.036$ ) and the stiffness ( $P = 0.026$ ) and physical function ( $P = 0.021$ ) dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group. Compared to baseline, overall psychological well-being was significantly improved in both groups after treatment ( $P = 0.015$  and  $P = 0.0003$  in the low and high dose groups respectively), and again, a significant dose-response relationship was observed. We conclude that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a dose-dependant manner. Double blind, placebo-controlled studies are now warranted to confirm these results.

Phytomedicine. 2002 Dec;9(8):681-6

### **BROMELAIN IN BLUNT INJURIES OF THE LOCOMOTOR SYSTEM. A STUDY OF OBSERVED APPLICATIONS IN GENERAL PRACTICE.**

**METHOD:** In an open case observation study involving patients with blunt injuries to the musculoskeletal system, the efficacy and tolerability of high-dose Bromelain POS, a plant-derived enzyme preparation, were investigated. The investigating physician was an orthopedic surgeon who, in addition to the usual therapeutic measures, treated 59 of his patients with the bromelaine preparation. The duration of the application was determined by the nature and severity of the lesion, and varied between one and three weeks. The test criteria were swelling, pain at rest and during movement, and tenderness. These parameters were evaluated on the day of the injury and on five subsequent dates. **RESULTS:** Treatment with bromelaine resulted in a clear reduction in all four parameters tested. Both swelling and the symptoms of pain had improved appreciably at all evaluation time points as compared with baseline. The tolerability of the preparation was very good, and patient compliance was correspondingly high.

Fortschr Med. 1995 Jul 10;113(19):303-6

### **NATURAL TREATMENT OF CHRONIC RHINOSINUSITIS.**

Chronic rhinosinusitis (CRS) is one of the most common long-term illnesses in the United States, affecting approximately 14% of the population. CRS is a challenging condition to treat, partly due to its multifaceted, poorly understood pathophysiology. Treatment goals include maintaining open drainage and decreasing inflammation while improving tissue integrity and limiting causative factors. This review covers the etiology, pathology, and diagnosis of CRS, as well as mainstream and alternative treatments. Discussion of alternative therapeutics includes nutrients and botanicals (ascorbic acid, bromelain, N-acetylcysteine, quercetin, undecylenic acid, and *Urtica dioica* and other herbal medicines) and procedures (nasal irrigation and naso-sympatico treatments). The influences of diet and air quality on CRS are also discussed.

Altern Med Rev. 2006 Sep;11(3):196-207

### **TREATMENT WITH ORAL BROMELAIN DECREASES COLONIC INFLAMMATION IN THE IL-10-DEFICIENT MURINE MODEL OF INFLAMMATORY BOWEL DISEASE.**

Bromelain is a mixture of proteinases derived from pineapple stem that is marketed in health food stores as a "digestive aid". Orally administered bromelain was anecdotally reported to induce clinical and endoscopic remission of ulcerative colitis in two patients whose disease was refractory to multi-agent conventional medical therapy. However, the potential efficacy of bromelain in colitis has not yet been tested rigorously in either animals or humans. In this study, the clinical and histologic severity of inflammatory bowel disease (IBD) was determined in IL-10<sup>-/-</sup> mice treated orally with bromelain *in vivo*. Daily treatment with oral bromelain beginning at age 5 weeks decreased the incidence and severity of spontaneous colitis in C57BL/6 IL-10<sup>-/-</sup> mice. Bromelain also significantly decreased the clinical and histologic severity of colonic inflammation when administered to piroxicam-exposed IL-10<sup>-/-</sup> mice with established colitis. Proteolytically active bromelain was required for anti-inflammatory effects *in vivo*. Adverse effects of dermatitis, hair loss, and weight loss due to mucositis were rare, dose related, and were not seen in wild-type mice treated orally with up to 1,000 mg bromelain/kg/day for 18 weeks. Although the exact mechanisms by which exogenous proteinases affect bowel inflammation have not yet been determined, the results justify additional studies of this complementary biologically based approach to treatment of IBD.

Clin Immunol. 2005 Aug;116(2):135-42

### **ROLE OF BROMELAIN IN THE TREATMENT OF PATIENTS WITH PITYRIASIS LICHENOIDES CHRONICA.**

**OBJECTIVES:** Pityriasis lichenoides chronica (PLC) is a skin disease of unknown etiology. Uncertainty about the etiopathogenesis of this skin disease is the reason for the unpredictable and non optimal efficacy of therapies available for its

treatment. The aim of the present study was to evaluate the efficacy of bromelain, a crude aqueous extract of the stems and immature fruit of pineapple, in the treatment of PLC. MATERIALS AND METHODS: Eight patients (3 males and 5 females) with PLC were enrolled in the study and treated for three months with oral bromelain (40 mg 3 times a day for 1 month, 40 mg twice a day for 1 month and 40 mg/day for 1 month). RESULTS: All patients showed complete clinical recovery after treatment. In 12 months of follow up, two patients experienced relapse 5-6 months after suspension of therapy but responded to another brief cycle of therapy. No side effects were encountered during therapy. CONCLUSIONS: In conclusion bromelain can be considered an effective therapeutic option for PLC; its efficacy could be related to its anti-inflammatory, immunomodulatory and/or anti-viral properties.

J Dermatolog Treat. 2007;18(4):219-22

## Magnesium

### DIETARY MAGNESIUM INTAKE IN A NATIONAL SAMPLE OF US ADULTS.

Despite the role of magnesium in maintaining health, much of the US population has historically not consumed adequate amounts of magnesium. Furthermore, significant racial or ethnic disparities in magnesium intake exist. Our objective was to provide more recent data about magnesium intake in the U.S. population. We analyzed the 24-h dietary recall data from 4,257 participants aged  $\geq 20$  y from the National Health and Nutrition Examination Survey 1999-2000. The median intake of magnesium was 326 mg/d (mean 352 mg/d) among Caucasian men, 237 mg/d (mean 278 mg/d) among African American men, 297 mg/d (330 mg/d) among Mexican American men, 237 mg/d (mean 256 mg/d) among Caucasian women, 177 mg/d (mean 202 mg/d) among African American women, and 221 mg/d (mean 242 mg/d) among Mexican American women. Among men and women, Caucasians had significantly higher mean intakes of dietary magnesium than African Americans but not Mexican Americans. Magnesium intake decreased with increasing age ( $P$  for linear trend = 0.035 for Caucasians;  $P$  for linear trend  $< 0.001$  for African Americans and Mexican Americans). Men had higher intakes of magnesium than women for each of the three race or ethnic groups ( $P < 0.001$  in each group). Caucasian men, African American men and Caucasian women who used vitamin, mineral or dietary supplements consumed significantly more magnesium in their diets than did those who did not. Substantial numbers of US adults fail to consume adequate magnesium in their diets. Furthermore, racial or ethnic differences in magnesium persist and may contribute to some health disparities.

J Nutr. 2003 Sep;133(9):2879-82

### INTRAVENOUS MAGNESIUM SULPHATE RELIEVES MIGRAINE ATTACKS IN PATIENTS WITH LOW SERUM IONIZED MAGNESIUM LEVELS: A PILOT STUDY.

We tested the hypothesis that patients with an acute attack of migraine headache and low serum levels ( $< 0.54$  mmol/l) of ionized magnesium are more likely to respond to an intravenous infusion of magnesium sulphate ( $\text{MgSO}_4$ ) than patients with higher serum ionized magnesium levels. 2. Serum ionized magnesium levels were drawn immediately before infusion of 1 g of  $\text{MgSO}_4$  in 40 consecutive patients with an acute migraine headache. 3. Pain reduction of 50% or more as measured on a headache intensity verbal scale of 1 to 10, occurred within 15 min of infusion in 35 patients. In 21 patients, at least this degree of improvement or complete relief persisted for 24h or more. Pain relief lasted at least 24h in 18 of 21 patients (86%) with serum ionized magnesium levels below 0.54 mmol/l, and in 3 of 19 patients (16%) with ionized magnesium levels at or above 0.54 mmol/l ( $P < 0.001$ ). Mean ionized magnesium levels in patients with relief lasting for at least 24h were significantly lower than in patients with no relief or brief relief ( $P < 0.01$ ). 4. Measurement of serum ionized magnesium levels may be useful in identifying patients with migraine headaches who may respond to an intravenous infusion of  $\text{MgSO}_4$ .

Clin Sci (Lond). 1995 Dec;89(6):633-6

### INTRAVENOUS MAGNESIUM SULFATE RAPIDLY ALLEVIATES HEADACHES OF VARIOUS TYPES.

**BACKGROUND:** Circumstantial evidence points to the possible role of magnesium deficiency in the pathogenesis of headaches and has raised questions about the clinical utility of magnesium as a therapeutic regimen in some headaches. **METHODS:** We evaluated the efficacy of intravenous infusion of 1 gram of magnesium sulfate ( $\text{MgSO}_4$ ) for the treatment of patients with headaches and attempted to correlate clinical responses to the basal serum ionized magnesium ( $\text{IMg}^{2+}$ ) level. We also determined if patients with certain headache types exhibit low serum  $\text{IMg}^{2+}$  as opposed to total serum magnesium. Using a case-control comparison at an outpatient headache clinic, a consecutive sample of patients presenting with a moderate or severe headache of any type were included in the study. Of the 40 patients in the study (mean age 38.2  $\pm$  9.4 years; range 14 to 55; 11 men [39.2  $\pm$  7.3 years] and 29 women [37.8  $\pm$  10.2 years]), 16 patients had migraines without aura, 9 patients had cluster headaches, 4 patients had chronic tension-type headaches, and 11 had chronic migrainous headaches. Total serum magnesium was measured with atomic absorption spectroscopy and a Kodak Ektachem DT-60. Sensitive ion selective electrodes were utilized to measure serum  $\text{IMg}^{2+}$  and ionized calcium ( $\text{ICa}^{2+}$ );  $\text{ICa}^{2+}/\text{IMg}^{2+}$  ratios were calculated. **RESULTS:** Complete elimination of pain was observed in 80% of the patients within 15 minutes of infusion of  $\text{MgSO}_4$ . No recurrence or worsening of pain was observed within 24 hours in 56% of the patients. Patients treated with  $\text{MgSO}_4$  observed complete elimination of migraine-associated symptoms such as photophobia and phonophobia as well as nausea. Correlation was noted between immediate and 24-hour responses with the serum  $\text{IMg}^{2+}$  levels. Immediate pain relief was observed in 32 (80%) of 40 patients ( $P < 0.001$ ). In 18. of the 32 patients, pain relief persisted for at least 24 hours ( $P < 0.005$ ). Of these 18 patients, 16 (89%) had a low

serum IMg<sup>2+</sup> level. Total magnesium levels in contrast in all subjects were within normal range (0.70-0.99 mmol/L). No side effects were observed, except for a brief flushed feeling. Of the 8 patients with no relief, only 37.5% had a low IMg<sup>2+</sup> level. Patients demonstrating no return of headache or associated symptoms within 24 hours of intravenous MgSO<sub>4</sub> exhibited the lowest initial basal levels of IMg<sup>2+</sup>. Non-responders exhibited significantly elevated total magnesium levels compared to responders. Although most subcategories of headache types investigated (ie, migraine, cluster, chronic migrainous) exhibited low serum IMg<sup>2+</sup> during headache and prior to intravenous MgSO<sub>4</sub>, the patients with cluster headaches exhibited the lowest basal levels of IMg<sup>2+</sup> ( $P < 0.01$ ). All headache subjects except for the chronic tension group exhibited rather high serum ICa<sup>2+</sup>/IMg<sup>2+</sup> ratios ( $P < 0.01$ , compared to controls). **CONCLUSIONS:** Intravenous infusion of 1 gram of MgSO<sub>4</sub> results in rapid relief of headache pain in patients with low serum IMg<sup>2+</sup> levels. Measurement of serum IMg<sup>2+</sup> levels may have a practical application in many types of headache patients. Low serum and brain tissue ionized magnesium levels may precipitate headache symptoms in susceptible patients.

Headache. 1996 Mar;36(3):154-60

### **MAGNESIUM INTAKE AND THE METABOLIC SYNDROME: EPIDEMIOLOGIC EVIDENCE TO DATE.**

The importance of magnesium intake in relation to the metabolic syndrome has been increasingly recognized. Magnesium is an essential mineral, critical for a number of metabolic functions in the human body. The major dietary sources of magnesium intake include whole grains, legumes, nuts, and green leafy vegetables. Animal studies indicate a pivotal role of magnesium in glucose homeostasis and insulin secretion and action. Experimental and clinical studies suggest that magnesium intake may be inversely related to the risk of hypertension and type 2 diabetes mellitus, and may decrease blood triglyceride and increase high-density lipoprotein cholesterol levels. The purpose of this brief review is to summarize the epidemiologic data relating magnesium to the metabolic syndrome and to discuss the potential mechanisms.

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### **MAGNESIUM INTAKE AND INCIDENCE OF METABOLIC SYNDROME AMONG YOUNG ADULTS.**

**BACKGROUND:** Studies suggest that magnesium intake may be inversely related to risk of hypertension and type 2 diabetes mellitus and that higher intake of magnesium may decrease blood triglycerides and increase high-density lipoprotein (HDL) cholesterol levels. However, the longitudinal association of magnesium intake and incidence of metabolic syndrome has not been investigated. **METHODS AND RESULTS:** We prospectively examined the relations between magnesium intake and incident metabolic syndrome and its components among 4,637 Americans, aged 18 to 30 years, who were free from metabolic syndrome and diabetes at baseline. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program/Adult Treatment Panel III definition. Diet was assessed by an interviewer-administered quantitative food frequency questionnaire, and magnesium intake was derived from the nutrient database developed by the Minnesota Nutrition Coordinating Center. During the 15 years of follow-up, 608 incident cases of the metabolic syndrome were identified. Magnesium intake was inversely associated with incidence of metabolic syndrome after adjustment for major lifestyle and dietary variables and baseline status of each component of the metabolic syndrome. Compared with those in the lowest quartile of magnesium intake, multivariable-adjusted hazard ratio of metabolic syndrome for participants in the highest quartile was 0.69 (95% confidence interval [CI], 0.52 to 0.91;  $P$  for trend  $<0.01$ ). The inverse associations were not materially modified by gender and race. Magnesium intake was also inversely related to individual component of the metabolic syndrome and fasting insulin levels. **CONCLUSIONS:** Our findings suggest that young adults with higher magnesium intake have lower risk of development of metabolic syndrome.

Circulation. 2006 Apr 4;113(13):1675-82

### **ROLE OF DIETARY MAGNESIUM IN CARDIOVASCULAR DISEASE PREVENTION, INSULIN SENSITIVITY AND DIABETES.**

**PURPOSE OF REVIEW:** This review summarizes the evidence for benefits of magnesium on metabolic abnormalities, inflammatory parameters, and cardiovascular risk factors and related-potential mechanisms. Controversy due to contrasting results in the literature is also discussed. **RECENT FINDINGS:** Increased dietary magnesium intake confers protection against the incidence of diabetes, metabolic syndrome, hypertension, and cardiovascular disease. It ameliorates insulin resistance, serum lipid profiles, and lowers inflammation, endothelial dysfunction, oxidative stress, and platelet aggregability. Magnesium acts as a mild calcium antagonist on vascular smooth muscle tone, and on postreceptor insulin signaling; it is critically involved in energy metabolism, fatty acid synthesis, glucose utilization, ATPase functions, release of neurotransmitters, and endothelial cell function and secretion. Prospective studies, however, have found only a modest effect for dietary magnesium on incident pathologies. Furthermore, magnesium supplementation on glucose metabolism, blood lipid levels, and ischemic heart disease has given inconsistent results. **SUMMARY:** There is strong biological plausibility for the direct impact of magnesium intake on metabolic and cardiovascular risk factors, but in-vivo magnesium deficiency might play only a modest role. Reverse causality, the strong association between magnesium and other beneficial nutrients, or the possibility that people who choose magnesium-rich foods are more health-conscious may be confounding factors.

### **DIETARY MAGNESIUM INTAKE AND THE FUTURE RISK OF CORONARY HEART DISEASE (THE HONOLULU HEART PROGRAM).**

Magnesium (Mg) deficiency is believed to have adverse cardiovascular consequences that are broad and complex, although an association between dietary Mg intake and the risk of coronary heart disease (CHD) has not been clearly identified. The purpose of this study is to examine the relation between dietary Mg intake and future risk of CHD. Reported findings are based on dietary Mg intake in 7,172 men in the Honolulu Heart Program. Intake of Mg was recorded at baseline examinations that took place from 1965 to 1968 when the men were aged 45 to 68 years. In 30 years of follow-up, 1,431 incident cases of CHD were identified. Within 15 years after dietary assessment, the age-adjusted incidence decreased significantly from 7.3 to 4.0 per 1,000 person-years in the lowest (50.3 to 186 mg/day) versus highest (340 to 1,183 mg/day) quintiles of Mg intake ( $p < 0.001$ ). When adjustments were made for age and other nutrients (singly or combined), there was a 1.7- to 2.1-fold excess in the risk of CHD in the lowest versus highest quintiles ( $p < 0.001$ ). The excess risk ranged from 1.5- to 1.8-fold after further adjustment for other cardiovascular risk factors ( $p < 0.05$ ). Associations between dietary Mg and coronary events occurring after 15 years of follow-up were modest. We conclude that the intake of dietary Mg is associated with a reduced risk of CHD. Whether increases in dietary Mg intake can alter the future risk of disease warrants further study.

Am J Cardiol. 2003 Sep 15;92(6):665-9

### **MAGNESIUM OROTATE IN SEVERE CONGESTIVE HEART FAILURE (MACH).**

**BACKGROUND:** Aim of this study was to evaluate adjuvant magnesium orotate on mortality and clinical symptoms in patients with severe heart failure under optimal cardiovascular medication. **METHODS:** In a monocentric, controlled, double-blind study, 79 patients with severe congestive heart failure (NYHA IV) under optimal medical cardiovascular treatment were randomised to receive either magnesium orotate (6,000 mg for 1 month, 3,000 mg for about 11 months,  $n=40$ ) or placebo ( $n=39$ ). Both groups were comparable in demographic data, duration of heart failure and pre- and concomitant treatment. **RESULTS:** After mean treatment duration of 1 year (magnesium orotate:  $364.1 \pm 14.7$  days, placebo:  $361.2 \pm 12.7$  days) the survival rate was 75.7% compared to 51.6% under placebo ( $p < 0.05$ ). Clinical symptoms improved in 38.5% of patients under magnesium orotate, whereas they deteriorated in 56.3% of patients under placebo ( $p < 0.001$ ). **CONCLUSION:** Magnesium orotate may be used as adjuvant therapy in patients on optimal treatment for severe congestive heart failure, increasing survival rate and improving clinical symptoms and patient's quality of life.

Int J Cardiol. 2008 Feb 15

### **MAGNESIUM AND C-REACTIVE PROTEIN IN HEART FAILURE: AN ANTI-INFLAMMATORY EFFECT OF MAGNESIUM ADMINISTRATION?**

**BACKGROUND:** Little is known about the relationship between serum magnesium (Mg) and C-reactive protein (CRP) in heart failure (HF). **AIM OF THE STUDY:** To investigate the relationship, if any, between serum Mg and CRP in HF patients and, concomitantly, to test a hypothesis that Mg supplementation might affect serum CRP levels. **METHODS:** Serum Mg and CRP were evaluated in 68 patients with chronic systolic HF leading to hospital admission and 65 patients requiring hospitalization for other causes. Following 5 weeks, serum Mg, CRP and intracellular Mg were reevaluated in 17 HF patients after administration of oral Mg citrate 300 mg/day (group A), and 18 untreated HF patients (group B). In order to obtain Gaussian distribution, logarithmic transformation of CRP was performed. **RESULTS:** Inverse correlation was found between serum Mg and log CRP ( $r = -0.28$ ,  $P = 0.002$ ). Compared to controls, patients with HF demonstrated higher baseline CRP levels, independent of coexisting conditions, and lower serum Mg values. Following Mg treatment, log CRP decreased from  $1.4 \pm 0.4$  to  $0.8 \pm 0.3$  in group A ( $P < 0.001$ ). No significant changes in log CRP were demonstrable in group B. Serum Mg (mmol/l) rose significantly in group A ( $0.74 \pm 0.04$ - $0.88 \pm 0.08$ ,  $P < 0.001$ ), and to a lesser extent in group B ( $0.82 \pm 0.08$ - $0.88 \pm 0.08$ ,  $P = 0.04$ ). Intracellular Mg significantly increased only in Mg-treated group A ( $P = 0.01$ ). **CONCLUSIONS:** Oral Mg supplementation to HF patients significantly attenuates blood levels of CRP, a biomarker of inflammation. Targeting the inflammatory cascade by Mg administration might prove a useful tool for improving the prognosis in HF.

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