

**ABSTRACTS****Mediterranean diet****N-3 FATTY ACIDS AND CANCER THERAPY.**

Supplementing the diet of tumor-bearing mice or rats with oils containing (n-3) (omega-3) or with purified (n-3) fatty acids has slowed the growth of various types of cancers, including lung, colon, mammary, and prostate. The efficacy of cancer chemotherapy drugs such as doxorubicin, epirubicin, CPT-11, 5-fluorouracil, and tamoxifen, and of radiation therapy has been improved when the diet included (n-3) fatty acids. Some potential mechanisms for the activity of (n-3) fatty acids against cancer include modulation of eicosanoid production and inflammation, angiogenesis, proliferation, susceptibility for apoptosis, and estrogen signaling. In humans, (n-3) fatty acids have also been used to suppress cancer-associated cachexia and to improve the quality of life. In one study, the response to chemotherapy therapy was better in breast cancer patients with higher levels of (n-3) fatty acids in adipose tissue [indicating past consumption of (n-3) fatty acids] than in patients with lower levels of (n-3) fatty acids. Thus, in combination with standard treatments, supplementing the diet with (n-3) fatty acids may be a nontoxic means to improve cancer treatment outcomes and may slow or prevent recurrence of cancer. Used alone, an (n-3) supplement may be a useful alternative therapy for patients who are not candidates for standard toxic cancer therapies.

J Nutr. 2004 Dec;134 (12 Suppl):3427S-3430S

**OMEGA-3 FATTY ACIDS AND INFLAMMATION.**

Dietary omega-3 (n-3) fatty acids have a variety of anti-inflammatory and immune-modulating effects that may be of relevance to atherosclerosis and its clinical manifestations of myocardial infarction, sudden death, and stroke. The n-3 fatty acids that appear to be most potent in this respect are the long-chain polyunsaturates derived from marine oils, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and this review is restricted to these substances. A variety of biologic effects of EPA and DHA have been demonstrated from feeding studies with fish or fish oil supplements in humans and animals. These include effects on triglycerides, high-density lipoprotein cholesterol, platelet function, endothelial and vascular function, blood pressure, cardiac excitability, measures of oxidative stress, pro- and anti-inflammatory cytokines, and immune function. Epidemiologic studies provide evidence for a beneficial effect of n-3 fatty acids on manifestations of coronary heart disease and ischemic stroke, whereas randomized, controlled, clinical feeding trials support this, particularly with respect to sudden cardiac death in patients with established disease. Clinically important anti-inflammatory effects in man are further suggested by trials demonstrating benefits of n-3 fatty acids in rheumatoid arthritis, psoriasis, asthma, and inflammatory bowel disorders. Given the evidence relating progression of atherosclerosis to chronic inflammation, the n-3 fatty acids may play an important role via modulation of the inflammatory processes.

Curr Atheroscler Rep. 2004 Nov;6(6):461-7

**EFFECT OF A MEDITERRANEAN-STYLE DIET ON ENDOTHELIAL DYSFUNCTION AND MARKERS OF VASCULAR INFLAMMATION IN THE METABOLIC SYNDROME: A RANDOMIZED TRIAL.**

**CONTEXT:** The metabolic syndrome has been identified as a target for dietary therapies to reduce risk of cardiovascular disease; however, the role of diet in the etiology of the metabolic syndrome is poorly understood. **OBJECTIVE:** To assess the effect of a Mediterranean-style diet on endothelial function and vascular inflammatory markers in patients with the metabolic syndrome. **DESIGN, SETTING, AND PATIENTS:** Randomized, single-blind trial conducted from June 2001 to January 2004 at a university hospital in Italy among 180 patients (99 men and 81 women) with the metabolic syndrome, as defined by the Adult Treatment Panel III. **INTERVENTIONS:** Patients in the intervention group (n = 90) were instructed to follow a Mediterranean-style diet and received detailed advice about how to increase daily consumption of whole grains, fruits, vegetables, nuts, and olive oil; patients in the control group (n = 90) followed a prudent diet (carbohydrates, 50%-60%; proteins, 15%-20%; total fat, <30%). **MAIN OUTCOME MEASURES:** Nutrient intake; endothelial function score as a measure of blood pressure and platelet aggregation response to L-arginine; lipid and glucose parameters; insulin sensitivity; and circulating levels of high-sensitivity C-reactive protein (hs-CRP) and interleukins 6 (IL-6), 7 (IL-7), and 18 (IL-18). **RESULTS:** After 2 years, patients following the Mediterranean-style diet consumed more foods rich in monounsaturated fat, polyunsaturated fat, and fiber and had a lower ratio of omega-6 to omega-3 fatty acids. Total fruit, vegetable, and nuts intake (274 g/d), whole grain intake (103 g/d), and olive oil consumption (8 g/d) were

also significantly higher in the intervention group ( $P < .001$ ). The level of physical activity increased in both groups by approximately 60%, without difference between groups ( $P = .22$ ). Mean (SD) body weight decreased more in patients in the intervention group (-4.0 [1.1] kg) than in those in the control group (-1.2 [0.6] kg) ( $P < .001$ ). Compared with patients consuming the control diet, patients consuming the intervention diet had significantly reduced serum concentrations of hs-CRP ( $P = .01$ ), IL-6 ( $P = .04$ ), IL-7 ( $P = 0.4$ ), and IL-18 ( $P = 0.3$ ), as well as decreased insulin resistance ( $P < .001$ ). Endothelial function score improved in the intervention group (mean [SD] change, +1.9 [0.6];  $P < .001$ ) but remained stable in the control group (+0.2 [0.2];  $P = .33$ ). At 2 years of follow-up, 40 patients in the intervention group still had features of the metabolic syndrome, compared with 78 patients in the control group ( $P < .001$ ). **CONCLUSION:** A Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome and its associated cardiovascular risk.

JAMA. 2004 Sep 22;292(12):1440-6

### **ADHERENCE TO A MEDITERRANEAN DIET AND SURVIVAL IN A GREEK POPULATION.**

**BACKGROUND:** Adherence to a Mediterranean diet may improve longevity, but relevant data are limited. **METHODS:** We conducted a population-based, prospective investigation involving 22,043 adults in Greece who completed an extensive, validated, food-frequency questionnaire at base line. Adherence to the traditional Mediterranean diet was assessed by a 10-point Mediterranean-diet scale that incorporated the salient characteristics of this diet (range of scores, 0 to 9, with higher scores indicating greater adherence). We used proportional-hazards regression to assess the relation between adherence to the Mediterranean diet and total mortality, as well as mortality due to coronary heart disease and mortality due to cancer, with adjustment for age, sex, body-mass index, physical-activity level, and other potential confounders. **RESULTS:** During a median of 44 months of follow-up, there were 275 deaths. A higher degree of adherence to the Mediterranean diet was associated with a reduction in total mortality (adjusted hazard ratio for death associated with a two-point increment in the Mediterranean-diet score, 0.75 [95% confidence interval, 0.64 to 0.87]). An inverse association with greater adherence to this diet was evident for both death due to coronary heart disease (adjusted hazard ratio, 0.67 [95% confidence interval, 0.47 to 0.94]) and death due to cancer (adjusted hazard ratio, 0.76 [95% confidence interval, 0.59 to 0.98]). Associations between individual food groups contributing to the Mediterranean-diet score and total mortality were generally not significant. **CONCLUSIONS:** Greater adherence to the traditional Mediterranean diet is associated with a significant reduction in total mortality.

N Engl J Med. 2003 Jun 26;348(26):2599-608

## **ADHD**

### **UPDATE ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

**PURPOSE OF REVIEW:** Attention-deficit/hyperactivity disorder (ADHD) is present in 3% to 10% of children in the United States. Children with ADHD can have academic impairments, social dysfunction, and poor self-esteem. There is also a higher risk of both cigarette smoking and substance abuse. Given this, the importance of treatment for ADHD needs to be underscored. This article will briefly review the diagnosis, etiology, and treatment of ADHD, with particular focus on nonstimulant medication and alternative treatment modalities. **RECENT FINDINGS:** Recent evidence suggests that the overall rate of medication treatment for ADHD has been increasing, with over 2 million children being treated with stimulants in 1997. With this increase, controversy has arisen over the possible association of stimulants with growth suppression. In addition, estimates indicate that as many as 30% of children with ADHD either do not respond to stimulant treatment or cannot tolerate the treatment secondary to side effects. This has led to the consideration of treatment with both nonstimulant medications as well as alternative therapies, including diet, iron supplementation, herbal medications, and neurofeedback. Considering the various treatment options now available for ADHD, along with the complexity of the condition, clinical practice guidelines are emerging for the treatment of ADHD and will be discussed. **SUMMARY:** ADHD continues to be a serious health problem. Adequate treatment is needed to avoid academic impairments, social dysfunction, and poor self-esteem. This treatment includes consideration of stimulant medication, nonstimulant medication, as well as alternative therapies. The child with ADHD is likely better served with a multimodal treatment plan, including medication, parent/school counseling, and behavioral therapy. Implementing an evidenced based algorithm for the treatment of ADHD may prove to be most effective.

Curr Opin Pediatr. 2004 Apr;16(2):217-26

### **IS ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AN ENERGY DEFICIENCY SYNDROME?**

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable yet clinically heterogeneous syndrome associated with hypocatecholamine function in subcortical and prefrontal cortical regions and clinical response to medications that enhance catecholamine function. The goal of this article is to present a hypothesis about the etiology of ADHD by synthesizing these findings with recent experiments indicating that activity-dependent neuronal energy consumption is regulated by cortical

astrocytes. The scientific literature was searched from 1966 to the present using MEDLINE and relevant key words. Inattention and impulsivity may be related to hypofunctionality of catecholamine projection pathways to prefrontal cortical areas, resulting in decreased neuronal energy availability. This may be mediated by astrocyte catecholamine receptors that normally regulate energy availability during neuronal activation. At least some forms of ADHD may be viewed as cortical, energy-deficit syndromes secondary to catecholamine-mediated hypofunctionality of astrocyte glucose and glycogen metabolism, which provides activity-dependent energy to cortical neurons. Several tests of this hypothesis are proposed.

Biol Psychiatry. 2001 Aug 1;50(3):151-8

### **OUTCOME-BASED COMPARISON OF RITALIN VERSUS FOOD-SUPPLEMENT TREATED CHILDREN WITH AD/HD.**

Twenty children with attention deficit/hyperactivity disorder (AD/HD) were treated with either Ritalin (10 children) or dietary supplements (10 children), and outcomes were compared using the Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT) and the WINKS two-way analysis of variance with repeated measures and with Tukey multiple comparisons. Subjects in both groups showed significant gains ( $p$  less than 0.01) on the IVA/CPT's Full Scale Response Control Quotient and Full Scale Attention Control Quotient ( $p$  less than 0.001). Improvements in the four sub-quotients of the IVA/CPT were also found to be significant and essentially identical in both groups: Auditory Response Control Quotient ( $p$  less than 0.001), Visual Response Control Quotient ( $p$  less than 0.05), Auditory Attention Quotient ( $p$  less than 0.001), and Visual Attention Quotient ( $p$  less than 0.001). Numerous studies suggest that biochemical heterogeneous etiologies for AD/HD cluster around at least eight risk factors: food and additive allergies, heavy metal toxicity and other environmental toxins, low-protein/high-carbohydrate diets, mineral imbalances, essential fatty acid and phospholipid deficiencies, amino acid deficiencies, thyroid disorders, and B-vitamin deficiencies. The dietary supplements used were a mix of vitamins, minerals, phytonutrients, amino acids, essential fatty acids, phospholipids, and probiotics that attempted to address the AD/HD biochemical risk factors. These findings support the effectiveness of food supplement treatment in improving attention and self-control in children with AD/HD and suggest food supplement treatment of AD/HD may be of equal efficacy to Ritalin treatment.

Altern Med Rev. 2003 Aug;8(3):319-30

### **EFFICACY OF THEOPHYLLINE COMPARED TO METHYLPHENIDATE FOR THE TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A PILOT DOUBLE-BLIND RANDOMIZED TRIAL.**

Attention-deficit hyperactivity disorder (ADHD) is a common disorder of childhood that affects 3-6% of school children. Conventional stimulant medications are recognized as useful symptomatic treatments by both specialists and parents. Nevertheless, approximately 30% of ADHD children treated with them do not respond adequately or cannot tolerate the associated adverse effects. Such difficulties highlight the need for alternative, safe and effective medications in the treatment of this disorder. Theophylline is a psychomotor stimulant most widely used as a broncodilator. Purinergic modulation may be therapeutically beneficial in the treatment of psychiatric disorders. We hypothesized that theophylline would be beneficial for the treatment of ADHD and report results of a trial of theophylline compared with methylphenidate for the treatment of ADHD. A total of 32 children with ADHD as defined by DSM IV were randomized to theophylline and methylphenidate dosed on an age and weight-adjusted basis at 4 mg/kg/day (under 12 years) and 3 mg/kg/day theophylline (over 12 years) (group 1) and 1 mg/kg/day methylphenidate (group 2) for a 6-week double-blind and randomized clinical trial. The principal measure of the outcome was the Teacher and Parent ADHD Rating Scale. Patients were assessed by a child psychiatrist, at baseline and at 14, 28, and 42 days after start of the medication. No significant differences were observed between theophylline and methylphenidate on the Parent and Teacher Rating Scale scores over the trial ( $t = 0.49$ ,  $d.f. = 24$   $P = 0.62$  and  $t = 0.19$ ,  $d.f. = 24$   $P = 0.54$  respectively). Although the number of dropouts in the methylphenidate group was higher than the theophylline group, there was no significant difference between the two protocols in terms of the dropouts. In addition, headaches were observed more often in the methylphenidate group. The results suggest that theophylline may be a useful for the treatment of ADHD. In addition, a tolerable side-effect profile is one of the advantages of theophylline in the treatment of ADHD. Nevertheless, our study is small and our results would need to be confirmed in a larger study.

Clin Pharm Ther. 2004 Apr;29(2):139-44

## ABSTRACTS

### Grape seed extract

#### **INTRACELLULAR MEDIATORS OF PROCYANIDIN-INDUCED LIPOLYSIS IN 3T3-L1 ADIPOCYTES.**

We have previously reported that grape seed procyanidins stimulate long-term lipolysis on 3T3-L1 fully differentiated adipocytes. To unravel the molecular mechanism by which procyanidins exert this effect, we checked the involvement of two main cellular targets in adipose cells: protein kinase A (PKA) and peroxisome proliferator-activated receptor-gamma (PPAR-gamma). Procyanidin treatment increased intracellular cAMP levels in 3T3-L1 adipocytes, and their lipolytic effect was inhibited by simultaneous treatment with H89, a PKA specific inhibitor. BRL49653, a very highly specific ligand of PPAR-gamma, totally abolished the lipolytic effect of procyanidins. Simultaneous to this long-term lipolytic effect, the mRNA levels of some differentiation adipocyte markers decreased, although there were no changes in the triglyceride content of the cells. BRL49653 did not antagonize the decrements of differentiation markers. These results support a mediation of PPAR-gamma and PKA on the lipolytic effects of procyanidins on 3T3-L1 adipocytes.

J Agric Food Chem. 2005 Jan 26;53(2):262-6

#### **GRAPE SEED PROANTHOCYANIDINS EXTRACT PROMOTES BONE FORMATION IN RAT'S MANDIBULAR CONDYLE.**

We studied the effect of dietary supplementation with grape seed proanthocyanidins extract (GSPE) 3 mg added in 100 g high-calcium diet with a calcium content of 1697 mg 100 g(-1) on mandibular condyle bone debility, which was induced by a low-calcium diet. Forty Wistar male rats, 5 week old, were randomly divided into control (Co), low-calcium diet (LC), low-calcium/high-calcium diet (LCH), and low-calcium/high-calcium with supplementary GSPE diet (LCHG) groups for 6 wk. Bone formation of the mandibular condyle was measured using peripheral quantitative computed tomography (pQCT). Significant differences were not seen among the four groups for body weight, measured weekly. The LCHG group scored significantly higher in cortical bone density, total bone cross-sectional area, cortical bone cross-sectional area, cortical bone mineral content, total bone density, total bone mineral content, and in the stress-strain index to the reference axis x when compared with the LCH group. We concluded that a high-calcium diet combined with GSPE supplementation is more effective in reversing mandibular condyle bone debility in rats than is a low-calcium diet, standard diet, or high-calcium diet alone.

Eur J Oral Sci. 2005 Feb;113(1):47-52

#### **PHARMACOLOGICAL PRECONDITIONING WITH RESVERATROL: ROLE OF CREB-DEPENDENT BCL-2 SIGNALING VIA ADENOSINE A3 RECEPTOR ACTIVATION.**

Recent studies demonstrated that resveratrol, a grape-derived polyphenolic phytoalexin, provides pharmacological preconditioning (PC) of the heart through a NO-dependent mechanism. Because adenosine receptors play a role in PC, we examined whether they play any role in resveratrol PC. Rats were randomly assigned to groups perfused for 15 min with 1) Krebs-Henseleit bicarbonate buffer (KHB) only; 2) KHB containing 10 microM resveratrol; 3) 10 microM resveratrol + 1 microM 8-cyclopentyl-1,3-dimethylxanthine (CPT; adenosine A(1) receptor blocker); 4) 10 microM resveratrol + 1 microM 8-(3-chlorostyryl) caffeine (CSC; adenosine A(2a) receptor blocker); 5) 10 microM resveratrol + 1 microM 3-ethyl-5-benzyl-2-methyl-4-phenylethynyl-6-phenyl-1,4-(+/-)-dihydropyridine-3,5-dicarboxylate (MRS-1191; adenosine A(3) receptor blocker); or 6) 10 microM resveratrol + 3 microM 2-(4-morpholinyl)-8-phenyl-1(4H)-benzopyran-4-one hydrochloride [LY-294002, phosphatidylinositol (PI)3-kinase inhibitor], and groups perfused with adenosine receptor blockers alone. Hearts were then subjected to 30-min ischemia followed by 2-h reperfusion. The results demonstrated significant cardioprotection with resveratrol evidenced by improved ventricular recovery and reduced infarct size and cardiomyocyte apoptosis. CPT and MRS 1191, but not CSC, abrogated the cardioprotective abilities of resveratrol, suggesting a role of adenosine A(1) and A(3) receptors in resveratrol PC. Resveratrol induced expression of Bcl-2 and caused its phosphorylation along with phosphorylation of cAMP response element-binding protein (CREB), Akt, and Bad. CPT blocked phosphorylation of Akt and Bad without affecting CREB, whereas MRS 1191 blocked phosphorylation of all compounds, including CREB. LY-294002 partially blocked the cardioprotective abilities of resveratrol. The results indicate that resveratrol preconditions the heart through activation of adenosine A(1) and A(3) receptors, the former transmitting a survival signal through PI3-kinase-Akt-Bcl-2 signaling pathway and the latter protecting the heart through a CREB-dependent Bcl-2 pathway in addition to an Akt-Bcl-2 pathway.

Am J Physiol Heart Circ Physiol. 2005 Jan;288(1):H328-35

## RESVERATROL: PREVENTING PROPERTIES AGAINST VASCULAR ALTERATIONS AND AGEING.

Cardiovascular diseases are the leading cause of death in developed countries where the common pathological substrate underlying this process is atherosclerosis. Several new concepts have emerged in relation to mechanisms that contribute to the regulation of the vascular diseases and associated inflammatory effects. Recently, potential antioxidants (vitamin E, polyphenols) have received much attention as potential anti-atherosclerotic agents. Among the polyphenols with health beneficial properties, resveratrol, a phytoalexin of grape, seem to be a good candidate protecting the vascular walls from oxidation, inflammation, platelet aggregation, and thrombus formation. In this review, we focus on the mechanism of resveratrol cardiovascular beneficial effects. We analyze, in relation with the different steps of atherosclerotic process, the resveratrol properties at multiple levels, such as cellular signaling, enzymatic pathways, apoptosis, and gene expression. We show and discuss the relationship with reactive oxygen species, regulation of pro-inflammatory genes including cyclooxygenases and cytokines in molecular inflammatory and aging processes, and how the regulation of these activities by resveratrol can lead to a prevention of vascular diseases.

Mol Nutr Food Res. 2005 Apr 14

## Diabetes

### ADVANCED GLYCATION ENDPRODUCTS—ROLE IN PATHOLOGY OF DIABETIC COMPLICATIONS.

Diabetes mellitus is a common endocrine disorder characterised by hyperglycaemia and predisposes to chronic complications affecting the eyes, blood vessels, nerves and kidneys. Hyperglycaemia has an important role in the pathogenesis of diabetic complications by increasing protein glycation and the gradual build-up of advanced glycation endproducts (AGEs) in body tissues. These AGE form on intra- and extracellular proteins, lipids, nucleic acids and possess complex structures that generate protein fluorescence and cross-linking. Protein glycation and AGE are accompanied by increased free radical activity that contributes towards the biomolecular damage in diabetes. There is considerable interest in receptors for AGEs (RAGE) found on many cell types, particularly those affected in diabetes. Recent studies suggest that interaction of AGEs with RAGE alter intracellular signalling, gene expression, release of pro-inflammatory molecules and free radicals that contribute towards the pathology of diabetic complications. This review introduces the chemistry of glycation and AGEs and examines the mechanisms by which they mediate their toxicity. The role of AGEs in the pathogenesis of retinopathy, cataract, atherosclerosis, neuropathy, nephropathy, diabetic embryopathy and impaired wound healing are considered. There is considerable interest in anti-glycation compounds because of their therapeutic potential. The mechanisms and sites of action of selected inhibitors, together with their potential in preventing diabetic complications are discussed.

Diabetes Res Clin Pract. 2005 Jan;67(1):3-21

### INCIDENCE OF NEWLY DIAGNOSED DIABETES ATTRIBUTABLE TO ATYPICAL ANTIPSYCHOTIC MEDICATIONS.

**OBJECTIVE:** The purpose of the study was to determine the proportion of patients with schizophrenia with a stable regimen of antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis. **METHOD:** Patients with schizophrenia for whom a stable regimen of antipsychotic monotherapy was consistently prescribed during any 3-month period between June 1999 and September 2000 and who had no diabetes were followed through September 2001 by using administrative data from the Department of Veterans Affairs. Cox proportional hazards models were developed to identify the characteristics associated with newly diagnosed diabetes and ketoacidosis. **RESULTS:** Of the 56,849 patients identified, 4,132 (7.3%) developed diabetes and 88 (0.2%) were hospitalized for ketoacidosis. Diabetes risk was highest for clozapine (hazard ratio=1.57) and olanzapine (hazard ratio=1.15); the diabetes risks for quetiapine (hazard ratio=1.20) and risperidone (hazard ratio=1.01) were not significantly different from that for conventional antipsychotics. The attributable risks of diabetes mellitus associated with atypical antipsychotics were small, ranging from 0.05% (risperidone) to 2.03% (clozapine). **CONCLUSIONS:** Although clozapine and olanzapine have greater diabetes risk, the attributable risk of diabetes mellitus with atypical antipsychotics is small.

Am J Psychiatry. 2004 Sep;161(9):1709-11

### HYPERGLYCEMIA ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT IN A MULTICENTER DRUG SAFETY PROJECT.

The introduction of new antipsychotics has resulted in the availability of drugs with improved safety and tolerability as well as proven efficacy compared to the older antipsychotics. New compounds might show new or different adverse effects that arise in the post-marketing phase when a greater number of patients are treated. One goal of the drug safety program in psychiatry AMSP (Arzneimittelsicherheit in der Psychiatrie) is the detection and description of severe, new, or rare adverse drug reactions (ADRs). Between 1993 and 2000, 122,562 patients were monitored in 35 psychiatric institutions, 86,349 patients of which

received antipsychotics. Hyperglycemia related to antipsychotics was observed in association with only two compounds so far: clozapine and olanzapine (clozapine 2 cases, olanzapine 7 cases). In 6 of 9 patients, weight gain preceded hyperglycemia. The relative frequency of these adverse drug related events was 0.013% for clozapine and 0.075% for olanzapine. The symptomatology included reversible hyperglycemia, worsening of existing diabetes, and new-onset diabetes. Control for glycaemic dysregulation should be maintained in clinical practice with these drugs.

Pharmacopsychiatry. 2004 Mar;37 Suppl 1:S79-83

### **DAILY STRESS AND GLYCAEMIC CONTROL IN TYPE 1 DIABETES: INDIVIDUAL DIFFERENCES IN MAGNITUDE, DIRECTION, AND TIMING OF STRESS-REACTIVITY.**

The aim of this study was to investigate the relationships between daily stress and glycaemic control in 54 people with Type 1 diabetes over 21 days. Measures included daily reports of stress (hassles), four-times-daily blood glucose measurements, and HbA1c levels. Time-series analyses revealed considerable variation between individuals in the nature and extent of blood glucose response to stress (stress-reactivity). In approximately one-third of the sample, stress was significantly associated with either same- or next-day blood glucose levels ( $r$ -range: -0.79 to 0.58). The majority of stress-reactive individuals (20.4% of the sample) demonstrated a positive association between hassles and same-day blood glucose levels. A much less common effect was found in two individuals (3.7%), where hassles were related to decreased same-day blood glucose. 'Stress-reactive' individuals tended to have high HbA1c values at baseline ( $t(52) = 2.2$ ;  $P < 0.05$ ), and significant relationships between emotion-focused coping and blood glucose levels ( $r = 0.93$ ;  $P < 0.01$ ). In conclusion, although a significant majority of this sample was resistant to the effects of stress, marked individual differences were found in the nature and extent of stress-reactivity. Our study goes beyond other published results as it is longitudinal, uses time-series analyses and includes a relatively larger sample. Clinicians need to be aware of these individual differences in order to advise patients about anticipating and preventing stress-related disruptions of glycaemic control.

Diabetes Res Clin Pract. 2004 Dec;66(3):237-44

### **MODERATE ALCOHOL INTAKE AND MARKERS OF INFLAMMATION AND ENDOTHELIAL DYSFUNCTION AMONG DIABETIC MEN.**

**AIMS/HYPOTHESIS:** Type 2 diabetes mellitus is characterised by heightened inflammation and endothelial dysfunction. Moderate alcohol intake has been associated with a reduced risk of cardiovascular disease in type 2 diabetic patients. It remains to be determined whether there is an association between alcohol and inflammation in individuals with diabetes. **METHODS:** We investigated the relationship between alcohol intake and inflammation in 726 of 18,159 men who returned blood samples in the Health Professionals Follow-up Study and had confirmed type 2 diabetes at blood draw. **RESULTS:** In age-adjusted analyses, alcohol intake was associated with lower levels of HbA1c, fibrinogen, soluble tumour necrosis factor receptor-2 (sTNF-R2) and soluble vascular adhesion molecule-1 (sVCAM-1), and with higher levels of HDL cholesterol and adiponectin ( $p$  value for trends  $< 0.05$ ). After adjustment for age, HbA1c, insulin use, fasting status, smoking, BMI, physical activity, aspirin use, prevalence of cardiovascular disease and dietary factors, each additional drink per day was related to increased HDL cholesterol (0.053 mmol/l,  $p < 0.0001$ ) and adiponectin (0.8 microg/ml,  $p = 0.01$ ), and decreased sTNFR-2 (73 pg/ml,  $p = 0.03$ ), fibrinogen (0.302 micromol/l,  $p = 0.02$ ) and sVCAM-1 (33 ng/ml,  $p = 0.02$ ). The relationship between alcohol and inflammatory biomarkers persisted when subjects were stratified according to HbA1c levels. **CONCLUSIONS/INTERPRETATION:** Moderate alcohol intake may have a beneficial effect on markers of inflammation and endothelial dysfunction in type 2 diabetic patients.

Diabetologia. 2004 Oct;47(10):1760-7

### **ACUTE ALCOHOL CONSUMPTION IMPROVES INSULIN ACTION WITHOUT AFFECTING INSULIN SECRETION IN TYPE 2 DIABETIC SUBJECTS.**

**OBJECTIVE:** Long-term exposure to alcohol is associated with an improvement in insulin sensitivity. At this time, however, there is no definitive proof that alcohol per se has an effect on the insulin sensitivity index (S(i)) in type 2 diabetes patients. The aim of the present study was to assess the role of acute moderate alcohol intake on insulin sensitivity and insulin secretion in comparable subjects with and without type 2 diabetes. **RESEARCH DESIGN AND METHODS:** Frequently sampled intravenous glucose tolerance tests (FSIGTs) were performed twice on eight healthy and eight type 2 diabetic volunteers. Forty grams of alcohol (vodka 40% wt/vol) or tap water were sipped from time -60 min to the end of the FSIGT. **RESULTS:** Lactate area under the curve (AUC) was higher in both groups during the alcohol study than in the control study. Free fatty acid (FFA) AUC was higher in type 2 diabetic subjects than in control subjects; alcohol slightly reduced FFA by 17% in control subjects ( $34 \pm 4$  mmol. min<sup>-1</sup>).  $I(-1)$ ;  $P = 0.1$ ) but significantly decreased FFA by 23% in type 2 diabetic subjects ( $54 \pm 10$ ;  $P = 0.007$ ). Beta-cell response was markedly reduced in type 2 diabetic subjects regardless of the type of study. Alcohol significantly increased S(i) in both groups. **CONCLUSIONS:** Acute alcohol consumption improves insulin action without affecting beta-cell secretion. This effect may be partly due to the inhibitory effect of alcohol on lipolysis. Alcohol intake increases insulin sensitivity and may partly explain both the J-shaped relationship between the prevalence of diabetes and the amount of alcohol consumption and the

decreased mortality for myocardial infarction.

Diabetes Care. 2004 Jun;27(6):1369-74

## ABSTRACTS

### Fibromyalgia

#### A REVIEW OF FIBROMYALGIA.

Characterized by chronic widespread joint and muscle pain, fibromyalgia is a syndrome of unknown etiology. The American College of Rheumatology's classification criteria for fibromyalgia include diffuse soft tissue pain of at least 3 months' duration and pain on palpation in at least 11 of 18 paired tender points. Symptoms are often exacerbated by exertion, stress, lack of sleep, and weather changes. Fibromyalgia is primarily a diagnosis of exclusion, established only after other causes of joint or muscle pain are ruled out. The initial workup for patients who present with widespread musculoskeletal pain should include a complete blood count, erythrocyte sedimentation rate, liver function tests, hepatitis C antibody, calcium, and thyrotropin. The musculoskeletal system, the neuroendocrine system, and the central nervous system, particularly the limbic system, appear to play major roles in the pathogenesis of fibromyalgia. The goal in treating fibromyalgia is to decrease pain and to increase function without promoting polypharmacy. Brief interdisciplinary programs have been shown to improve subjective pain. Fibromyalgia is a complex syndrome associated with significant impairment on quality of life and function and substantial financial costs. Once the diagnosis is made, providers should aim to increase patients' function and minimize pain. This can be accomplished through nonpharmacological and pharmacological interventions. With proper management, the rate of disability appears to be significantly reduced.

Am J Manag Care. 2004 Nov;10(11 Pt 1):794-800

#### INVESTIGATION OF THE HYPOTHALAMO-PITUITARY-ADRENAL AXIS (HPA) BY 1 MICROG ACTH TEST AND METYRAPONE TEST IN PATIENTS WITH PRIMARY FIBROMYALGIA SYNDROME.

Primary fibromyalgia syndrome (PFS) is characterized by widespread chronic pain that affects the musculoskeletal system, fatigue, anxiety, sleep disturbance, headache and postural hypotension. The pathophysiology of PFS is unknown. The hypothalamic-pituitary-adrenal (HPA) axis seems to play an important role in PFS. Both hyperactivity and hypoactivity of the HPA axis have been reported in patients with PFS. In this study we assessed the HPA axis by 1 microg ACTH stimulation test and metyrapone test in 22 patients with PFS and in 15 age-, sex-, and body mass index (BMI)- matched controls. Metyrapone (30 mg/kg) was administered orally at 23:00 h and blood was sampled at 08:30 h the following morning for 11-deoxycortisol. ACTH stimulation test was carried out by using 1 microg (iv) ACTH as a bolus injection after an overnight fast, and blood samples were drawn at 0, 30 and 60 min. Peak cortisol level (659.4 +/- 207.2 nmol/l) was lower in the patients with PFS than peak cortisol level (838.7 +/- 129.6 nmol/l) in the control subjects ( $p < 0.05$ ). Ten patients (45%) with PFS had peak cortisol responses to 1 microg ACTH test lower than the lowest peak cortisol detected in healthy controls. After metyrapone test 11-deoxycortisol level was 123.7 +/- 26 nmol/l in patients with PFS and 184.2 +/- 17.3 nmol/l in the controls ( $p < 0.05$ ). Ninety five percent of the patients with PFS had lower 11-deoxycortisol level after metyrapone than the lowest 11-deoxycortisol level after metyrapone detected in healthy controls. We also compared the adrenal size of the patients with that of the healthy subjects and we found that the adrenal size between the groups was similar. This study clearly shows that HPA axis is underactivated in PFS, rather than overactivated.

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#### CLINICAL ENDOCANNABINOID DEFICIENCY (CECD): CAN THIS CONCEPT EXPLAIN THERAPEUTIC BENEFITS OF CANNABIS IN MIGRAINE, FIBROMYALGIA, IRRITABLE BOWEL SYNDROME AND OTHER TREATMENT-RESISTANT CONDITIONS?

**OBJECTIVES:** This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis. **METHODS:** Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources. **RESULTS:** Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT<sub>1A</sub> and inhibits 5-HT<sub>2A</sub> receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging. **CONCLUSION:** Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological

patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.

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### **PSYCHOLOGICAL STRESS AND FIBROMYALGIA: A REVIEW OF THE EVIDENCE SUGGESTING A NEUROENDOCRINE LINK.**

The present review attempts to reconcile the dichotomy that exists in the literature in relation to fibromyalgia, in that it is considered either a somatic response to psychological stress or a distinct organically based syndrome. Specifically, the hypothesis explored is that the link between chronic stress and the subsequent development of fibromyalgia can be explained by one or more abnormalities in neuroendocrine function. There are several such abnormalities recognised that both occur as a result of chronic stress and are observed in fibromyalgia. Whether such abnormalities have an aetiologic role remains uncertain but should be testable by well-designed prospective studies.

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### **NEUROENDOCRINE ABNORMALITIES IN FIBROMYALGIA.**

Fibromyalgia is a disorder of unknown etiology characterized by chronic, widespread musculoskeletal pain and symptoms such as fatigue, poor sleep, gastrointestinal complaints, and psychologic problems that are similar to those experienced by patients with hormone deficiencies. This review summarizes the available data on the neuroendocrine function in fibromyalgia, including data on hormone secretion, circadian phase, and autonomic nervous system function. Studies suggest that there may be lower activity of a number of hypothalamic-pituitary-peripheral gland axes and altered autonomic nervous system function in patients with fibromyalgia. These reductions in activity are mild to moderate and do not result from alterations in circadian rhythms. The reduced hormonal and autonomic responses appear to reflect an impairment in the hypothalamic or central nervous system response to stimuli rather than a primary defect at the level of the pituitary gland or the peripheral glands. A combination of multiple, mild impaired responses may lead to more profound physiologic and clinical consequences as compared with a defect in only one system, and could contribute to the symptoms of fibromyalgia.

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