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## Journal ABSTRACTS

### Theanine

#### **GREEN TEA EXTRACT AND CATECHIN AMELIORATE CHRONIC FATIGUE-INDUCED OXIDATIVE STRESS IN MICE.**

Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often accompanied by numerous symptoms involving various body systems. The etiology of CFS remains unclear, but a number of studies have shown that oxidative stress may be involved in its pathogenesis. The present study was designed to investigate the protective effect of green tea extract (GTE) and catechin in the mouse model of CFS. Animals were subjected to a forced swimming test session of 6 minutes every day for 7 days; a significant increase in immobility time on successive days represented the CFS in mice. Biochemical analysis revealed that the chronic swim test significantly increased lipid peroxidation levels and decreased glutathione levels in mouse whole-brain homogenate. Treatment with GTE (25 or 50 mg/kg, i.p.) and catechin (50 or 100 mg/kg, i.p.) for 7 days reversed the increase in immobility time. Protection was correlated with the lowered levels of lipid peroxidation and restoration of reduced glutathione levels in the brains of fatigued mice. These findings strongly suggest the pivotal role of oxidative stress in the pathophysiology of CFS and that GTE and catechin could be used as potential agents in the management of CFS and warrant the inclusion of GTE and catechin in the treatment regimen of CFS patients.

*J Med Food.* 2005 Spring;8(1):47-52

#### **FRAGRANCES IN OOLONG TEA THAT ENHANCE THE RESPONSE OF GABAA RECEPTORS.**

We electrophysiologically investigated the effect of some fragrant compounds in oolong tea on the response of ionotropic gamma-aminobutyric acid (GABA) receptors (GABAA receptors) which were expressed in *Xenopus* oocytes. Of the tested fragrances in oolong tea, cis-jasmone, jasmine lactone, linalool oxide and methyl jasmonate significantly potentiated the response. Among these, cis-jasmone and methyl jasmonate potently potentiated the response, having a respective dissociation constant of the compound ( $K_p$ ) and maximum potentiation ( $V_m$ ) of 0.49 mM and 322% for cis-jasmone, and 0.84 mM and 450% for methyl jasmonate. Inhalation of 0.1% cis-jasmone or methyl jasmonate significantly increased the sleeping time of mice induced by pentobarbital, suggesting that these fragrant compounds were absorbed by the brain and thereby potentiated the GABAA receptor response. Both of these compounds may therefore have a tranquilizing effect on the brain.

*Biosci Biotechnol Biochem.* 2004 Sep;68(9):1842-8

#### **SUPPRESSIVE EFFECT OF GREEN TEA CATECHINS ON MORPHOLOGIC AND FUNCTIONAL REGRESSION OF THE BRAIN IN AGED MICE WITH ACCELERATED SENESCENCE (SAMP10).**

Green tea catechins (GT-catechins) have been reported to have an antioxidative effect. We investigated the effect of long-term GT-catechin intake on aging and oxidative damage using aged mice with accelerated senescence (SAMP10), a model of brain senescence with cerebral atrophy and cognitive dysfunction. Major atrophy was observed in the rhinencephalon, hippocampus and striatum of 12-month-old untreated SAMP10 mice. Similarly, levels of 8-oxodeoxyguanosine (8-oxodG), a marker of oxidative DNA damage, were higher in these parts of the cerebrum than in the cerebral cortex and liver. GT-catechin intake effectively suppressed such atrophy in 12-month-old SAMP10 mice. A preventive effect of GT-catechin intake on oxidative DNA damage was also observed in the rhinencephalon (an area particularly susceptible to atrophy) at 6 months of age, i.e. during the early stages of atrophy. A suppressive effect of GT-catechin intake on cognitive dysfunction, as determined by the learning time needed to acquire an avoidance response and assessments of working memory in a Y-maze, was also found in 12-month-old mice. These results suggest that GT-catechin intake partially improves the morphologic and functional alterations that occur naturally in the brains of aged SAMP10 mice.

*Exp Gerontol.* 2004 Jul;39(7):1027-34

#### **DAILY TEA DRINKING IS ASSOCIATED WITH A LOW LEVEL OF DEPRESSIVE SYMPTOMS IN THE FINNISH**

## GENERAL POPULATION.

Tea drinking has been suggested to be beneficial in neurodegenerative diseases where depressive mood is a common symptom. Nevertheless, it is not known whether there are any associations between tea drinking and depression in general populations. In this study we investigated these associations in a sample of the Finnish general population (n = 2011) using a postal questionnaire and the Beck Depression Inventory (BDI). Those who reported drinking tea daily were less depressed than the others. They had a lower mean BDI score and also a lower prevalence of depression. None of those whose daily tea intake was five cups or more had depression. Several potential confounding factors were included in the final sex- and age-adjusted multivariate logistic regression model which suggested that those who drink tea daily may have a significantly reduced risk of being depressed (adjusted odds ratio 0.47, 95% confidence interval 0.27-0.83). In conclusion, an inverse relationship between daily tea drinking and the risk of being depressed was found in a relatively large general population sample. Nevertheless, the underlying mechanisms are unresolved and further studies are needed.

*Eur J Epidemiol.* 2005;20(4):359-63

### **BLACK AND GREEN TEA POLYPHENOLS ATTENUATE BLOOD PRESSURE INCREASES IN STROKE-PRONE SPONTANEOUSLY HYPERTENSIVE RATS.**

Oxidative stress was reported to be involved not only in cardiovascular diseases, but also in hypertension. Epidemiologic studies indicated that tea consumption slightly reduces blood pressure. We conducted two studies to determine whether black and green tea can lower blood pressure (BP) in stroke-prone spontaneously hypertensive rats (SHRSP). Male SHRSP (n=15) were allowed to recover for 2 wk after a transmitter for measuring BP was implanted in the peritoneal cavity. The rats were divided into three groups: the control group consumed tap water (30 mL/d); the black tea polyphenol group (BTP) consumed water containing 3.5 g/L thearubigins, 0.6 g/L theaflavins, 0.5 g/L flavonols and 0.4 g/L catechins; and the green tea polyphenol group (GTP) consumed water containing 3.5 g/L catechins, 0.5 g/L flavonols and 1 g/L polymetric flavonoids. The telemetry system was used to measure BP, which were recorded continuously every 5 min for 24 h. During the daytime, systolic and diastolic BP were significantly lower in the BTP and GTP groups than in the controls. Protein expressions of catalase and phosphorylated myosin light chain (MLC-p) were measured in the aorta by Western blotting. GTP significantly increased catalase expression, and BTP and GTP significantly decreased MLC-p expression in the aorta. These data demonstrate that both black and green tea polyphenols attenuate blood pressure increases through their antioxidant properties in SHRSP. Furthermore, because the amounts of polyphenols used in this experiment correspond to those in approximately 1 L of tea, the regular consumption of black and green tea may also provide some protection against hypertension in humans.

*J Nutr.* 2004 Jan;134(1):38-42

### **EFFECTS OF THEANINE ON ALCOHOL METABOLISM AND HEPATIC TOXICITY.**

We previously showed that theanine, is a major amino acid in green tea, enhanced doxorubicin (DOX) induced antitumor activity. Besides, theanine induced the elevation of glutathione (GSH) level attributable to the increase of glutamate in the liver of mice, namely theanine would reduce the adverse reaction of DOX. Consequently, theanine was thought to be effective against the tissue changes with GSH level reduction. On the other hand, it is suggested excessive uptake of alcohol causes a production of free radicals, a decrease of GSH level, and an increase in the amount of lipid peroxide (LPO) in liver, and shifting to an alcoholic liver injury. Then, aiming at the prevention and medical treatment of a hepatic toxicity by the food components with little toxicity, we have studied the effect of theanine (i.p.) on ethanol metabolism and hepatic toxicity using ethanol (p.o.) single-administered mice. On the 1st hour after ethanol administration, the ethanol concentrations in blood of the theanine combined groups decreased compared with the ethanol-alone group. The alcohol dehydrogenase and aldehyde dehydrogenase activities in the liver increased by combined theanine. Since the elevation of cytochrome P450 (CYP) 2E1 activity was controlled in the theanine-combined groups, it was considered that these disorders attributable to CYP2E1 in ethanol long-term uptake might be avoidable by theanine. Although LPO increased in 3 h after by single-administration of ethanol, the increase was controlled by theanine-administration and was improved until the normal level. In conclusion, it was indicated that theanine was effective against alcoholic liver injury.

*Biol Pharm Bull.* 2005 Sep;28(9):1702-6

### **NUTRITIONAL FACTORS AND GASTRIC CANCER IN ZHOUSHAN ISLANDS, CHINA.**

**AIM:** To investigate the association between nutrient intakes and high incidence rate of gastric cancer among residents in Zhoushan Islands. **METHODS:** A frequency-matched design of case-control study was used during the survey on dietary factors and gastric cancer in Zhoushan Islands, China. A total of 103 cases of gastric cancer diagnosed in 2001 were included in the study and 133 controls were randomly selected from the residents in Zhoushan Islands. A food frequency questionnaire was specifically designed for the Chinese dietary pattern to collect information on dietary intake. A computerized database of the dietary and other relative information of each participant was completed. Total calories and 15 nutrients were calculated according to the food composition table and their adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by gender using unconditional logistic regression models. **RESULTS:** High intakes of protein, saturated fat, and cholesterol were observed with the increased risk of gastric cancer particularly among males (OR(Q4 vs Q1) were 10.3, 3.24, 2.76 respectively). While carbohydrate was a significant high-risk nutrient (OR(Q4 vs Q1) = 14.8; P for linear trend = 0.024) among females. Regardless of their gender, the cases reported significantly higher daily intake of sodium mainly from salts. As to the nutrients of vitamins A and C, an inversed association with the risk of GC was found. Baseline characteristics of participants were briefly described. **CONCLUSION:** The findings from this study confirm the role of diet-related exposure in the etiology of gastric cancer from the point of view of epidemiology. An increased risk of gastric cancer is associated with high intakes of protein, saturated fat, cholesterol and sodium, while consumption of polyunsaturated fat, vitamin A and ascorbic acid may have a protective effect against gastric cancer.

*World J Gastroenterol.* 2005 Jul 28;11(28):4311-6

### **ANTIOXIDANT STATUS AND RISK OF CANCER IN THE SU.VI.MAX STUDY: IS THE EFFECT OF SUPPLEMENTATION DEPENDENT ON BASELINE LEVELS?**

The Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study, a randomised double-blind, primary-prevention trial showed that after 7.5 years, low-dose antioxidant supplementation lowered the total cancer incidence in men, but not in women. To explain this difference in the impact of antioxidant supplementation in men and women, we hypothesised that the effect of supplementation is dependent on initial antioxidant status; 12 741 French adults (7713 females aged 35-60 years; 5028 males aged 45-60 years) received daily antioxidant supplementation (120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 microg Se, 20 mg Zn daily) or a matching placebo. Cut-off limits for baseline serum concentrations of the different antioxidant vitamins and minerals were defined as follows for both men and women: 0.3 micromol/l for beta-carotene, 11.4 micromol/l for vitamin C, 15 micromol/l for vitamin E, 0.75 micromol/l for Se and 10.7 micromol/l for Zn. The percentage of men with serum concentrations under cut-off limits was higher for vitamins C and E and beta-carotene in those who developed a cancer than in those who did not. The risk of cancer was higher in men with baseline concentrations of serum vitamin C or vitamin E under cut-off limits, but not in women. The effect of supplementation was greater in men with baseline serum concentrations of vitamin C, vitamin E and beta-carotene below the cut-off limits compared with those above it. This effect was maintained only for vitamin E after adjustment for age, tobacco, and alcohol consumption and BMI. No effect of supplementation could be seen in women. Baseline antioxidant status is related to the risk of cancer in men but not in women and therefore does not entirely explain the differences observed in the effect of antioxidant supplementation on cancer risk between sexes in the SU.VI.MAX study.

*Br J Nutr.* 2005 Jul;94(1):125-32

### **ADVANCED GLYCATION END PRODUCTS IN DIABETES-ASSOCIATED ATHEROSCLEROSIS AND RENAL DISEASE: INTERVENTIONAL STUDIES.**

There is increasing evidence that advanced glycation end products (AGEs) and their interactions with various receptors (in particular, the receptor RAGE) play a pivotal role in the development and progression of diabetic macro- and microvascular complications. Several approaches have been used to inhibit tissue accumulation of AGEs in diabetes, including inhibitors of AGE formation such as aminoguanidine, ALT 946, and pyridoxamine-or putative cross-link breakers such as ALT 711. Alternative interventions have also included the administration of a soluble receptor for RAGE, sRAGE, thus capturing circulating AGEs and preventing them from binding to the cell-bound full-length receptor RAGE, thereby inhibiting the proinflammatory and profibrotic response following AGE-RAGE binding. In this review we summarize the evidence for such antiglycation therapies in retarding or delaying the development and progression of diabetes-associated atherosclerosis and renal disease while focusing on

interventional strategies inhibiting AGE accumulation. In summary, all approaches have been shown to confer some degree of antiatherosclerotic and renoprotective effects, albeit to different degrees and by different mechanisms.

*Ann N Y Acad Sci.* 2005 Jun;1043:759-66

### **CARNOSINE AND CARNOSINE-RELATED ANTIOXIDANTS: A REVIEW.**

First isolated and characterized in 1900 by Gulewitsch, carnosine (beta-alanyl-L-histidine) is a dipeptide commonly present in mammalian tissue, and in particular in skeletal muscle cells; it is responsible for a variety of activities related to the detoxification of the body from free radical species and the by-products of membrane lipids peroxidation, but recent studies have shown that this small molecule also has membrane-protecting activity, proton buffering capacity, formation of complexes with transition metals, and regulation of macrophage function. It has been proposed that carnosine could act as a natural scavenger of dangerous reactive aldehydes from the degradative oxidative pathway of endogenous molecules such as sugars, polyunsaturated fatty acids (PUFAs) and proteins. In particular, it has been recently demonstrated that carnosine is a potent and selective scavenger of alpha,beta-unsaturated aldehydes, typical by-products of membrane lipids peroxidation and considered second messengers of the oxidative stress, and inhibits aldehyde-induced protein-protein and DNA-protein cross-linking in neurodegenerative disorders such as Alzheimer's disease, in cardiovascular ischemic damage, in inflammatory diseases. The research for new and more potent scavengers for HNE and other alpha,beta-unsaturated aldehydes has produced a consistent variety of carnosine analogs, and the present review will resume, through the scientific literature and the international patents, the most recent developments in this field.

*Curr Med Chem.* 2005;12(20):2293-315

### **ADVANCED GLYCATION IN HEALTH AND DISEASE: ROLE OF THE MODERN ENVIRONMENT.**

It is believed that intracellular and extracellular advanced glycation (AGEs) or lipoxidation end products (ALEs), together with dysregulated glucose and lipid metabolism, are important contributors to oxidant or carbonyl stress, enhanced cellular redox-sensitive transcription factor activity, and impaired innate immune defense, causing over time inappropriate inflammatory responses. However, neither the magnitude nor the persistent nature of this increased prooxidant state are completely understood. A significant correlation has been found between ingested and circulating AGEs in humans in recent years. Based on animal studies, the injurious impact of diet-derived AGEs to vascular and kidney tissues is estimated to rival or even exceed that caused by hyperglycemia or hyperlipidemia. Consistent with this view, dietary AGE restriction has been associated with suppression of several immune defects, insulin resistance, and diabetic complications, whether genetically or diet induced, despite persistent diabetes. These findings are in support of clinical evidence from subjects with diabetes or vascular or kidney disease. Most recently, evidence from animal studies points to AGE restriction as an effective means for extending median life span, similar to that previously shown by marked caloric restriction. We conclude that excessive AGE consumption, in the current dietary/social structure, represents an independent factor for inappropriate oxidant stress responses, which may promote the premature expression of complex diseases associated with adult life, such as diabetes and cardiovascular disease.

*Ann N Y Acad Sci.* 2005 Jun;1043:452-60

### **OXIDATIVE STRESS AND NEURODEGENERATION.**

Oxidative stress is a well-studied early response in chronic neurodegenerative diseases, including Alzheimer's disease, where neuronal loss can exceed 90% in the vulnerable neuronal population. Oxidative stress affects all classes of macromolecules (sugar, lipids, proteins, and DNA), leading inevitably to neuronal dysfunction. We observed that Nepsilon-(carboxymethyl)lysine (CML), the predominant advanced glycation end product that accumulates in vivo, along with its glycation-specific precursor hexitol-lysine, are increased in neurons from cases of Alzheimer's disease, especially those containing intracellular neurofibrillary pathology. The increase in hexitol-lysine and CML can result from either lipid peroxidation or advanced glycation, whereas hexitol-lysine is solely a product of glycation, suggesting that two distinct oxidative processes act in concert in the neuropathology of the disease. Furthermore, using olfactory neurons as an experimental model, we observed an increase in glycation products in neurons derived from Alzheimer's disease patients. Our findings support the idea that aldehyde-mediated modifications, in concert with oxyradical-mediated modifications, are critical early pathogenic factors in Alzheimer's disease.

*Ann N Y Acad Sci.* 2005 Jun;1043:545-52

### **ROLE OF GLUCOXIDATION AND LIPID OXIDATION IN THE DEVELOPMENT OF ATHEROSCLEROSIS.**

Previous data have indicated that modification of proteins/lipids by glucoxidation and/or lipid oxidation may initiate/propagate the formation of atherosclerotic plaques. Although the biomarker carboxymethyllysine (CML) has been detected in these lesions, the origin of the reactive oxygen species (ROS) leading to its formation and the source of its carbon backbone are unknown. As presented here, the stimulation of cultured monocytes by phorbol-12-myristate-13-acetate (TPA), an activator of protein kinase C

that can mimic the effects of high glucose, angiotensin II, and other physiological stimuli, leads to cellular ROS generation and concomitant formation of intracellular CML. Inhibitors of ROS-generating cellular systems such as NO synthase, xanthine oxidase, or cytochrome P450 oxidase had no effect on CML formation. Likewise, in cells with inactive NAD(P)H oxidase no reduced CML formation was found. In cells exhibiting a high glycolysis rate, CML formation was unaffected. Because we found rapid CML formation in the presence of unsaturated fatty acids, it appears that lipid oxidation is quantitatively more important. In vivo studies revealed strong intracellular CML staining in areas of histiocytic/monocytic infiltration or proliferation, mostly associated with atheroma formation. Corresponding CML staining patterns were found in healing wounds of different ages, indicating that formation of atherosclerosis is a chronic wound repair associated with a low-grade inflammatory reaction. In summary, CML is formed concomitantly with oxidative stress in activated monocytes and can be regarded as a biomarker for a low-grade inflammatory tissue reaction in the atherosclerotic plaque. Its formation via lipid oxidation may be involved in the development of atherosclerosis.

*Ann N Y Acad Sci.* 2005 Jun;1043:343-54

### **IS ATHEROSCLEROSIS A MULTIFACTORIAL DISEASE OR IS IT INDUCED BY A SEQUENCE OF LIPID PEROXIDATION REACTIONS?**

The delivery of not only free cholesterol but also cholesterol esters to cells by low-density lipoprotein (LDL) has hitherto been unstudied. Minor compounds present in mammalian-derived food include cholesterol linoleate and arachidonate. Evidence is presented that these esters are directly incorporated into VLDL and are responsible for the deleterious effects of atherosclerosis. Cholesterol esterified with these polyunsaturated fatty acids (PUFAs) is readily oxidized at the PUFA residue during storage and heating. Apparently, the liver is unable to distinguish between nonoxidized and oxidized cholesterol PUFA esters and also incorporates the latter into VLDL, which is transformed to LDL. When this LDL is transferred to endothelial cells, the toxic products are liberated and induce cell damage. Cell damage is combined with structural changes that influence neighboring cells and cause an influx of Ca<sup>2+</sup> ions and activation of phospholipases and lipoxygenases, resulting in production of lipid hydroperoxides (LOOHs). When the level of free PUFAs generated by phospholipases exceeds a certain limit, lipoxygenases commit suicide, causing liberation of iron ions. The latter react with LOOHs and thus induce a switch from enzymatic to nonenzymatic generation of lipid peroxidation (LPO) products. Although the LOO. radicals produced in enzymatic reactions are deactivated within the enzyme complex, LOO. radicals generated in nonenzymatic reactions are able to attack any biological compound, inducing severe damage. Apparently, iron ions and LOOH molecules at the surface of injured cells transfer the nonenzymatic LPO reactions to the phospholipid layer of bypassing lipoproteins, thus explaining why inflammatory diseases, such as diabetes, are combined with atherogenesis.

*Ann N Y Acad Sci.* 2005 Jun;1043:355-66

### **OXIDATIVE STRESS AND EXPERIMENTAL CARCINOGENESIS.**

The focus of this review is to provide state-of-the-art knowledge on the involvement of oxygen free radicals (OFR) in carcinogenesis with a particular reference to skin model system as the process of cancer development is best understood in this organ. However, a brief description of the role of OFR in other organs is also provided. The term OFR refers to forms of oxygen exhibiting high reactivity and having at least one unpaired electron. The role of OFR in different stages of carcinogenesis such as initiation, promotion and progression is described. Out of many mechanisms described for the chemical initiation of tumorigenesis, a number of them may involve free radicals in the cascade of reactions. Evidences that support the involvement of free radicals in tumor promotion include (i) a number of free radical-generating compounds are found to be tumor promoters in various animal model systems, (ii) ROS generating systems can mimic the biochemical action of tumor promoters, (iii) some tumor promoters stimulate the production of ROS, (iv) tumor promoters modulate the cellular antioxidant defense systems, and (v) free radical scavengers, detoxifiers and antioxidants inhibit the process of tumor promotion. The role of ROS in the progression stage of carcinogenesis is evident from the fact that a number of different free radical generating compounds enhance the malignant conversion of benign papillomas into carcinoma and their effectiveness may be related to the type of radicals produced into the biological system.

*Indian J Exp Biol.* 2002 Jun;40(6):656-67

### **THE AGE OF THE MATRIX: CHEMISTRY, CONSEQUENCE AND CURE.**

Accumulation of advanced glycation endproducts (AGEs) plays a crucial part in the development of age-related diseases and diabetic complications. AGEs are formed in vivo via the so-called Maillard reaction: a reducing sugar reacts with a protein to form a labile Amadori product that is subsequently stabilized, producing an irreversible, non-enzymatic post-translational modification of the protein involved. Recently, it has become clear that, in addition to sugars, lipids play an important role in the initiation of AGE formation, and that genetic factors contribute to an individual's AGE levels. The highest AGE levels are found in tissues with slow turnover, such as tendon, skin, bone, amyloid plaques and cartilage. AGEs exert their effects by adversely affecting the mechanical properties of the matrix and by modulating tissue turnover. In cartilage, these detrimental effects result in tissue that

is more prone to the development of osteoarthritis. As such, the accumulation of AGEs provides the first molecular mechanism explaining the age-related increase in the incidence of osteoarthritis. Ongoing research into anti-AGE-ing therapies, such as pyrodoxamine and thiazolium compounds, which are often developed to prevent AGE-induced diabetic complications, might also prove beneficial for the prevention of osteoarthritis.

*Curr Opin Pharmacol.* 2004 Jun;4(3):301-5

### **MOLECULAR TARGETS AND ANTICANCER POTENTIAL OF INDOLE-3-CARBINOL AND ITS DERIVATIVES.**

Indole-3-carbinol (I3C) is produced by members of the family Cruciferae, and particularly members of the genus Brassica (e.g., cabbage, radishes, cauliflower, broccoli, Brussels sprouts, and daikon). Under acidic conditions, I3C is converted to a series of oligomeric products (among which 3,3'-diindolylmethane is a major component) thought to be responsible for its biological effects in vivo. In vitro, I3C has been shown to suppress the proliferation of various tumor cells including breast cancer, prostate cancer, endometrial cancer, colon cancer, and leukemic cells; induce G1/S arrest of the cell cycle, and induce apoptosis. The cell cycle arrest involves downregulation of cyclin D1, cyclin E, cyclin-dependent kinase (CDK)2, CDK4, and CDK6 and upregulation of p15, p21, and p27. Apoptosis by I3C involves downregulation antiapoptotic gene products, including Bcl-2, Bcl-xL, survivin, inhibitor-of-apoptosis protein (IAP), X chromosome-linked IAP (XIAP), and Fas-associated death domain protein-like interleukin-1-beta-converting enzyme inhibitory protein (FLIP); upregulation of proapoptotic protein Bax; release of mitochondrial cytochrome C; and activation of caspase-9 and caspase-3. This agent inhibits the activation of various transcription factors including nuclear factor-kappaB, SP1, estrogen receptor, androgen receptor and nuclear factor-E2-related factor 2 (Nrf2). This indole potentiates the effects of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) through induction of death receptors and synergises with chemotherapeutic agents through downregulation of P-glycoprotein (P-gp). In vivo, I3C was found to be a potent chemopreventive agent for hormonal-dependent cancers such as breast and cervical cancer. These effects are mediated through its ability to induce apoptosis, inhibit DNA-carcinogen adduct formation, and suppress free-radical production, stimulate 2-hydroxylation of estradiol, inhibit invasion and angiogenesis. Numerous studies have indicated that I3C also has a strong hepatoprotective activity against various carcinogens. Initial clinical trials in women have shown that I3C is a promising agent against breast and cervical cancers.

*Cell Cycle*. 2005 Sep;4(9):1201-15

### **EFFECTS OF INDOLE-3-CARBINOL AND PHENETHYL ISOTHIOCYANATE ON COLON CARCINOGENESIS INDUCED BY AZOXYMETHANE IN RATS.**

Indole-3-carbinol (I3C) and phenethyl isothiocyanate (PEITC) are breakdown products of the glucosinolates glucobrassicin and gluconasturtiin, respectively, and are thought to reduce carcinogen activation by P450 enzymes. To assess the effects of these compounds on colon cancer risk, rats were divided into 5 groups and fed the following diets: control diet (AIN-93G), or diets with PEITC or I3C added to the control diet: High PEITC (3.37 mmols/kg diet -high level of PEITC), low PEITC (0.67 mmols/kg -low level of PEITC), high I3C (6.8 mmols/kg -high level of I3C), and low I3C (1.36 mmols/kg -low level of I3C). Diets were fed for 2 weeks before and 10 weeks after administration of the colon carcinogen azoxymethane. Precancerous lesion (aberrant crypt foci, ACF) number in the distal colon was significantly lower in both high I3C and low I3C groups (6.9 +/- 0.8 and 5.9 +/- 0.59 per cm (2), respectively) when compared to the control group (10.4 +/- 0.9). No significant difference in ACF number was found between either PEITC group and the control group. ACF expressing sialomucin, thought to indicate ACF more likely to progress to tumors, were greater in the high PEITC group (13 +/- 3) than the control (5.6 +/- 2). Mucin-depleted ACF, suggested to have the greatest tumorigenic potential, tended to be lower in the low I3C group (p<0.06) compared to the control group. Mucosal apoptotic and cell proliferation labeling indices did not differ among groups, suggesting that reduction in ACF number by I3C does not involve alterations in mucosal cell kinetics. No significant differences were found among the groups in hepatic cytochrome P450 2E1 (CYP2E1) activity, the first enzyme involved in activation of azoxymethane. However, there was increased activity of NADPH- and NADH reductases with high I3C, enzymes involved in the transfer of reducing equivalents to cytochrome P450. These results suggest that I3C lowers colon cancer risk through a mechanism not involving reduction of carcinogen activation by CYP2E1.

*Carcinogenesis*. 2005 Aug 19

### **3,3'-DIINDOLYLMETHANE, A CRUCIFEROUS VEGETABLE DERIVED SYNTHETIC ANTI-PROLIFERATIVE COMPOUND IN THYROID DISEASE.**

Considerable epidemiological evidence exists to link thyroid disease with differing patterns of dietary consumption, in particular, cruciferous vegetables. We have been studying the anti-thyroid cancer (TCa) activity of indole-3-carbinol (I3C) found in cruciferous vegetables and its acid catalyzed dimer, 3,3'-diindolylmethane (DIM). There are no studies as yet to elucidate the effect of these compounds on the altered proliferative patterns in goiter or thyroid neoplasia. In this study, we tested the anti-proliferative effects

of I3C and DIM on four different thyroid cancer cell lines representative of papillary (B-CPAP and 8505-C) and follicular carcinoma of the thyroid (CGTH-W-1 and ML-1), and primary human goiter cells. Cell survival and IC(50) values for I3C and DIM were calculated by the XTT assay and cell cycle distribution analysis was done by flow cytometry. DIM was found to be a better anti-proliferative agent than I3C in both papillary and follicular TCa resulting in a greater cytotoxic effect at a concentration over three fold lower than predicted by the molar ratio of DIM and I3C. The anti-proliferative activity of DIM in follicular TCa was mediated by a G1 arrest followed by induction of apoptosis. DIM also inhibited the growth of primary goiter cells by 70% compared to untreated controls. Contrary to traditional belief that cruciferous vegetables are "goitrogenic," DIM has anti-proliferative effects in glandular thyroid proliferative disease. Our preclinical studies provide a strong rationale for the clinical exploration of DIM as an adjuvant to surgery in thyroid proliferative disease.

*Biochem Biophys Res Commun.* 2005 Nov 25;337(3):1019-25

### **INDOLE-3-CARBINOL ACTIVATES THE ATM SIGNALING PATHWAY INDEPENDENT OF DNA DAMAGE TO STABILIZE P53 AND INDUCE G1 ARREST OF HUMAN MAMMARY EPITHELIAL CELLS.**

The phytochemical indole-3-carbinol (I3C), from cruciferous vegetables such as broccoli, has been shown to elicit a potent anti-proliferative response in human breast cancer cell lines. Treatment of the immortalized human mammary epithelial cell line MCF10A with I3C induced a G1 cell cycle arrest, elevated p53 tumor suppressor protein levels and stimulated expression of downstream transcriptional target, p21. I3C treatment also elevated p53 levels in several breast cancer cell lines that express mutant p53. I3C did not arrest MCF10A cells stably transfected with dominant-negative p53, establishing a functional requirement for p53. Cell fractionation and immunolocalization studies revealed a large fraction of stabilized p53 protein in the nucleus of I3C-treated MCF10A cells. With I3C treatment, phosphatidylinositol-3-kinase family member ataxia telangiectasia-mutated (ATM) was phosphorylated, as were its substrates p53, CHK2 and BRCA1. Phosphorylation of p53 at the N-terminus has previously been shown to disrupt the interaction between p53 and its ubiquitin ligase, MDM2, and therefore stabilizing p53. Coimmunoprecipitation analysis revealed that I3C reduced by 4-fold the level of MDM2 protein that associated with p53. The p53-MDM2 interaction and absence of p21 production were restored in cells treated with I3C and the ATM inhibitor wortmannin. Significantly, I3C does not increase the number of 53BP1 foci or H2AX phosphorylation, indicating that ATM is activated independent of DNA double-strand breaks. Taken together, our results demonstrate that I3C activates ATM signaling through a novel pathway to stimulate p53 phosphorylation and disruption of the p53-MDM2 interaction, which releases p53 to induce the p21 CDK inhibitor and a G1 cell cycle arrest.

*Int J Cancer.* 2005 Sep 8

### **3,3'-DIINDOLYLMETHANE INHIBITS ANGIOGENESIS AND THE GROWTH OF TRANSPLANTABLE HUMAN BREAST CARCINOMA IN ATHYMIC MICE.**

Studies have linked the consumption of broccoli and other cruciferous vegetables to a reduced risk of breast cancer. The phytochemical indole-3-carbinol (I3C), present in cruciferous vegetables, and its major acid-catalyzed reaction product 3,3'-diindolylmethane (DIM) have bioactivities relevant to the inhibition of carcinogenesis. In this study, the effect of DIM on angiogenesis and tumorigenesis in a rodent model was investigated. We found that DIM produced a concentration-dependent decrease in proliferation, migration, invasion and capillary tube formation of cultured human umbilical vein endothelial cells (HUVECs). Consistent with its antiproliferative effect, which was significant at only 5 microM DIM, this indole caused a G1 cell cycle arrest in actively proliferating HUVECs. Furthermore, DIM downregulated the expression of cyclin-dependent kinases 2 and 6 (CDK2, CDK6), and upregulated the expression of CDK inhibitor, p27(Kip1), in HUVECs. We observed further in a complementary in vivo Matrigel plug angiogenesis assay that, compared with vehicle control, neovascularization was inhibited up to 76% following the administration of 5 mg/kg DIM to female C57BL/6 mice. Finally, this dose of DIM also inhibited the growth of human MCF-7 cell tumor xenografts by up to 64% in female athymic (nu/nu) mice, compared with the vehicle control. This is the first study to show that DIM can strongly inhibit the development of human breast tumor in a xenograft model and to provide evidence for the antiangiogenic properties of this dietary indole.

*Carcinogenesis.* 2005 Apr;26(4):771-8

### **INNOVATIVE AGENTS IN CANCER PREVENTION.**

There are many facets to cancer prevention: a good diet, weight control and physical activity, a healthy environment, avoidance of carcinogens such as those in tobacco smoke, and screening of populations at risk to allow early detection. But there is also the possibility of using drugs or naturally occurring compounds to prevent initiation of, or to suppress, tumour growth. Only a few such agents have been used to date in the clinic with any success, and these include non-steroidal anti-inflammatory drugs for colon, finasteride for prostate and tamoxifen or raloxifene for breast tumours. An ideal chemopreventive agent would restore normal growth control to a preneoplastic or cancerous cell population by modifying aberrant signalling pathways or inducing apoptosis (or both) in cells beyond repair. Characteristics for such an agent include selectivity for damaged or transformed cells, good bioavailability and more than one mechanism of action to foil redundancy or crosstalk in signalling pathways. As more

research effort is being targeted towards this area, the distinction between chemotherapeutic and chemopreventive agents is blurring. Chemotherapeutic drugs are now being designed to target over- or under-active signalling molecules within cancer cells, a philosophy which is just as relevant in chemoprevention. Development of dietary agents is particularly attractive because of our long-standing exposure to them, their relative lack of toxicity, and encouraging indications from epidemiology. The carcinogenic process relies on the cell's ability to proliferate abnormally, evade apoptosis, induce angiogenesis and metastasise to distant sites. In vitro studies with a number of different diet-derived compounds suggest that there are molecules capable of modulating each of these aspects of tumour growth. However, on the negative side many of them have rather poor bioavailability. The challenge is to uncover their multiple mechanisms of action in order to predict their efficacy, to learn how to use them effectively in combination, and in some cases to redesign them to improve potency or bioavailability. These ideas are illustrated by dietary agents such as indole-3-carbinol (I3C), epigallocatechin gallate (EGCG), curcumin and resveratrol, all of which appear to have a number of different molecular targets, impinging on several signalling pathways. Ultimately it may be possible not only to suppress tumours and to extend quality of life by administering appropriate diet-derived molecules, but also to refine the definition of a cancer chemopreventive diet.

*Recent Results Cancer Res.* 2005;166:257-75

### **ANTI-CARCINOGENIC AND ANTI-METASTATIC PROPERTIES OF INDOLE-3-CARBINOL IN PROSTATE CANCER.**

Indole-3-carbinol (I3C), a compound present as glucobrassicin in cruciferous vegetables has anticancer activities which is in line with some of the epidemiological evidence that suggests a beneficial effect of consumption of cruciferous vegetables on cancer incidence and progression. The precise target of indole-3-carbinol has not been determined. We examined the effect of I3C on prostate cancer in a well-defined R3327 model using Copenhagen rats and the transplantable cell line, MAT-LyLu. This cell line derived from a tumor in Copenhagen rats is androgen independent and metastasizes to the lung and lymph nodes. Tumors were induced in Copenhagen rats by injecting MAT-LyLu subcutaneously and the animals treated with I3C that was administered either intraperitoneally or intravenously, in order to achieve maximal systemic exposure. This was a departure from the traditional chemopreventive route of indole-3-carbinol where the compound was incorporated in the diet. Our results indicate that I3C inhibited the incidence, growth and metastases of MAT-LyLu cells and both i.p. and i.v. injections of I3C were equally effective. Statistical analysis (Kaplan-Meier curves) clearly indicates a tumor-free and overall survival benefit as a result of treatment with I3C. These studies show for the first time that I3C in an injectible form has anti-prostate cancer activity.

*Oncol Rep.* 2005 Jan;13(1):89-93

### **INHIBITION OF NUCLEAR TRANSLOCATION OF NUCLEAR FACTOR- $\kappa$ B CONTRIBUTES TO 3,3'-DIINDOLYLMETHANE-INDUCED APOPTOSIS IN BREAST CANCER CELLS.**

Dietary indole-3-carbinol (I3C), a natural compound present in vegetables of the genus Brassica, showed clinical benefits and caused apoptosis in breast cancer cells. Our laboratory and others have shown that I3C induces apoptosis in breast cancer cells mediated by inactivation of Akt and nuclear factor-kappaB (NF-kappaB) pathway. 3,3'-Diindolylmethane (DIM), a major in vivo acid-catalyzed condensation product of I3C, also showed some benefit in breast cancer. However, the precise molecular mechanism(s) by which DIM induces apoptosis in breast cancer cells has not been fully elucidated. Hence, we investigated whether DIM-induced apoptosis of breast cancer cells could also be mediated by inactivation of Akt and NF-kappaB. We found that DIM induces apoptotic processes in MCF10A derived malignant (MCF10CA1a) cell lines but not in nontumorigenic parental MCF10A cells. DIM specifically inhibits Akt kinase activity and abrogates the epidermal growth factor-induced activation of Akt in breast cancer cells, similar to those observed for I3C. We also found that DIM reduces phosphorylation of I $\kappa$ B $\alpha$ , an inhibitor of NF-kappaB. Our confocal microscopy study clearly showed that DIM blocks the translocation of p65, a subunit of NF-kappaB to the nucleus. DNA binding analysis and transfection studies with I $\kappa$ B kinase cDNA revealed that overexpression of I $\kappa$ B kinase mediates I $\kappa$ B $\alpha$  phosphorylation, which activates NF-kappaB, and this activation was completely abrogated by DIM treatment. Taken together, these results showed for the first time that the inactivation of Akt and NF-kappaB activity also plays important roles in DIM-induced apoptosis in breast cancer cells, which seems to be more relevant to in vivo situations.

*Cancer Res.* 2005 Jan 1;65(1):364-71

### **MALE OSTEOPOROSIS: NEW TRENDS IN DIAGNOSIS AND THERAPY.**

Osteoporosis is a common condition in men affecting approximately 2 million males in the US. Compared with women, osteoporosis develops later in life and the incidence of osteoporosis-related fractures is lower in men. The morbidity and mortality associated with osteoporotic fractures are much greater in men compared with women, and secondary causes of osteoporosis are more frequently (in approximately 50% of cases) identified in men compared with women with osteoporosis. Excessive alcohol consumption, glucocorticoid excess and hypogonadism are the most commonly identified causes. Primary osteoporosis in men has been linked to changes in sex steroid secretion, the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis and the vitamin D-parathyroid hormone (PTH) 25-hydroxyvitamin D [25(OH)D]-PTH system. Diagnosing osteoporosis in men is complicated by an ongoing debate on whether to use sex-specific reference values for bone mineral density (BMD) or female reference values. The International Society for Clinical Densitometry recommended using a T score of -2.5 or less of male reference values to diagnose osteoporosis in men who are > or =65 years of age. However, this definition is yet to be validated in terms of fracture incidence and prevalence. Ensuring adequate calcium and vitamin D intake is the cornerstone of any regimen aimed at preventing or treating osteoporosis in men. Bisphosphonates are currently the therapy of choice for treatment of male osteoporosis. A short course of parathyroid hormone (1-34) [teriparatide] may be indicated for men with very low BMD or in those in whom bisphosphonate therapy is unsuccessful. The use of testosterone-replacement therapy for the prevention and treatment of male osteoporosis remains controversial but likely to benefit osteoporotic men with evident hypogonadism.

*Drugs Aging.* 2005;22(9):741-8

### **ANDROPAUSE: IS ANDROGEN REPLACEMENT THERAPY INDICATED FOR THE AGING MALE?**

The number of men in the United States > or =65 years of age is projected to increase from 14,452,000 in 2000 to 31,343,000 in 2030. Approximately 30% of men 60-70 years of age and 70% of men 70-80 years of age have low bioavailable or free testosterone levels. Symptoms and findings of testosterone deficiency are similar to those associated with aging. They include loss of energy, depressed mood, decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, frailty, osteopenia, and osteoporosis. Several small clinical trials indicate that testosterone replacement therapy can improve many of these findings; however, the studies have not been powered to assess potential risks, such as the need for invasive treatment of benign prostatic hyperplasia, development of a clinical prostate cancer, or cardiovascular events. Thus, the benefit/risk ratio of testosterone replacement therapy in aging men is not known.

*Annu Rev Med.* 2005;56:117-37

### **CLIMACTERIC MEDICINE: EUROPEAN MENOPAUSE AND ANDROPAUSE SOCIETY (EMAS) 2004/2005 POSITION STATEMENTS ON PERI- AND POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY.**

In women experiencing distressing climacteric symptoms during the peri- and postmenopause there is conclusive evidence from abundant randomised controlled trials that systemic hormone replacement therapy (HRT) of any type affords symptom relief, with no alternative treatment producing similar effect. Though this evidence is accumulating, the question of how to provide best clinical practice in an attempt to both alleviate the menopausal symptoms and prevent the more long-term postmenopausal degenerative diseases is still under debate. When providing climacteric medicine, the dose and regimen of HRT needs to be individualised based on the principle of choosing the lowest appropriate dose in relation to severity of symptoms and on the menopausal age. However, few long-term data on different HRT formulations exist in symptomatic women, which also account for baseline risk of cardiovascular disease (CVD), breast cancer and osteoporosis. In most cases, an individualized prescription together with life-style management will sustain possibilities for net beneficial effects on climacteric symptoms, quality of life (QoL), sexuality and osteoporosis, with only rare risk of severe adverse effects. With the perspective provided by recent epidemiological findings, not least from the estrogen only arm of the Women's Health Initiative Study (WHI), European Menopause and Andropause Society (EMAS) supports research activities in symptomatic women with new HRT formulations in order to affect positively the balance of clinical benefit and risk, including specific information on QoL and also account for the traditional differences in treatment modalities between the US and Europe, and the difference in BMI, life-style and diet. In women experiencing an early menopause (<45 year) current data support a specific overall benefit of HRT. At present, more long-term systemic HRT may be considered in women at high risk of osteoporotic fractures, in particular when alternate therapies are either inappropriate or insufficiently effective, as benefits will outweigh any risks. In contrast, urogenital symptoms may be addressed

efficiently and safely with long-term local estrogen therapy.

*Maturitas*. 2005 May 16;51(1):8-14

### **SMOKING AND HORMONES IN HEALTH AND ENDOCRINE DISORDERS.**

Smoking has multiple effects on hormone secretion, some of which are associated with important clinical implications. These effects are mainly mediated by the pharmacological action of nicotine and also by toxins such as thiocyanate. Smoking affects pituitary, thyroid, adrenal, testicular and ovarian function, calcium metabolism and the action of insulin. The major salient clinical effects are the increased risk and severity of Graves' hyperthyroidism and ophthalmopathy, osteoporosis and reduced fertility. Smoking also contributes to the development of insulin resistance and hence type 2 diabetes mellitus. An important concern is also the effect of smoking on the foetus and young children. Passive transfer of thiocyanate can cause disturbance of thyroid size and function. Furthermore, maternal smoking causes increased catecholamine production, which may contribute to under perfusion of the foetoplacental unit.

*Eur J Endocrinol*. 2005 Apr;152(4):491-9

### **RANDOMIZED TRIAL OF ETIDRONATE PLUS CALCIUM AND VITAMIN D FOR TREATMENT OF LOW BONE MINERAL DENSITY IN CROHN'S DISEASE.**

**BACKGROUND & AIMS:** Crohn's disease causes an increase in osteopenia and osteoporosis. This study assessed the efficacy of adding etidronate to calcium and vitamin D supplementation for treatment of low bone mineral density in Crohn's disease. **METHODS:** One hundred fifty-four patients with Crohn's disease with decreased bone mineral density, determined by using dual-energy x-ray absorptiometry, were randomly assigned to receive etidronate (400 mg orally) or not for 14 days; both groups were then given daily calcium (500 mg) and vitamin D (400 IU) supplementation for 76 days. This cycle was repeated 8 times during a period of 24 months. Biochemical characteristics and bone mineral densities were assessed at 6, 12, and 24 months. **RESULTS:** After 24 months bone mineral density significantly increased from baseline in both the etidronate- and the non-etidronate-treated groups (both groups receiving calcium and vitamin D supplementation) at the lumbar spine ( $P < .001$ ), ultradistal radius ( $P < .001$ ), and trochanter ( $P = .004$ ) sites, but not at the total hip. The increase in bone mineral density was similar in each treatment group. No bone mineral density differences were found when groups were analyzed according to gender, corticosteroid use, bone mineral density at baseline, or age. **CONCLUSIONS:** Low bone mineral density is frequently associated with Crohn's disease. Supplementation with daily calcium and vitamin D is associated with increases in bone mineral density. The addition of oral etidronate does not further enhance bone mineral density.

*Clin Gastroenterol Hepatol*. 2005 Feb;3(2):122-32

### **PROMOTING GENERAL HEALTH DURING ANDROGEN DEPRIVATION THERAPY (ADT): A RAPID 10-STEP REVIEW FOR YOUR PATIENTS.**

Androgen deprivation for prostate cancer use to be applied only in the latter stage of the disease process, thus, the issue of promoting general health during this time was not a concern because the subject of life and death was more paramount. However, thanks to earlier detection of prostate cancer, there has been a general stage migration in this disease. Men are choosing these traditionally late stage therapies earlier and earlier. Therefore, the subject of quality of life on this treatment has now garnered as much attention as the survival issues. Cognitive or mental health concerns, cholesterol changes, hot flashes, osteoporosis, and other side effects are being addressed and treated with a variety of conventional medicines. However, the issue of the role of the patient or what men can do personally to promote better mental and physical health is desperately needed in this area. A variety of beneficial lifestyle changes and over-the-counter agents may have an enormous impact on men's health during androgen deprivation. Calcium and vitamin D supplements, aerobic and resistance exercise, cholesterol awareness and reduction, weight loss, and other individual changes could have an enormous impact on the quality and quantity of a man's life. Some of these so called "bottom line" recommendations are reviewed in this article to empower the patient during this time, and to send clearly the message that he has a role to play apart from just picking up and using a prescription drug for side effects, and his role is just as critical for improving the probability of living longer and better.

*Urol Oncol*. 2005 Jan-Feb;23(1):56-64

### **EVIDENCE-BASED GUIDELINES FOR THE PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS: A CONSENSUS DOCUMENT OF THE BELGIAN BONE CLUB.**

Glucocorticoids (GCs) are frequently prescribed for various inflammatory and/or life-threatening conditions concerning many systems in the body. However, they can provoke many aftereffects, of which osteoporosis (OP) is one of the most crippling complications, with its host of fractures. The dramatic increase in bone fragility is mainly attributable to the GC-induced rapid bone loss in all skeletal compartments. We have reviewed the meta-analyses and randomized controlled studies reporting

medical therapeutic interventions currently registered in Belgium for the management of GC-OP comparatively with a placebo. Based on this research, an expert meeting developed a consensus on the prevention and therapy of GC-OP. The pathophysiology of GC-OP is complex. Several factors, acting separately or synergistically, have been described. Their great number could help to understand the rapidity of bone loss and of bone fragility occurrence, indicating that a rapid therapeutic intervention should be implemented to avoid complications. All patients on GCs are threatened with OP, so the prevention and/or therapy of GC-OP should be considered not only for postmenopausal females, but also for osteopenic premenopausal females and for males put on a daily dose of at least 7.5 mg equivalent prednisolone that is expected to last at least 3 months. Non-pharmacological interventions, such as exercise and avoidance of tobacco and alcohol, should be recommended, even if their role is not definitely settled in GC-OP prevention. Supplemental calcium and vitamin D should be considered as the first-line therapy because of the decrease in intestinal calcium absorption provoked by GCs. They also could be considered either as isolated therapy in patients taking less than 7.5 mg prednisolone daily and/or for a predicted period shorter than 3 months or as adjuvant therapy to other more potent drugs. Hormone replacement therapy could be considered in young postmenopausal females on GC, such as in postmenopausal OP, or in men with low androgen levels. Calcitonin appears to have a protective effect on trabecular bone in GC-OP, just as in postmenopausal OP. There is an increasing body of evidence supporting the antifracture efficacy of bisphosphonates, notably alendronate and risedronate. Preventative and curative therapy of GC-OP should be maintained as long as the patient is on GC treatment and could be stopped after weaning from GC, because there is more than circumstantial evidence of some recovery of BMD when GCs are stopped. There is no indication in GC-OP for any combination of two antiresorptive agents (except for calcium and vitamin D) or for an antiresorptive and an anabolic agent. There is indeed no proof that the increased costs of combined treatments will translate into increased therapeutic efficacy.

*Osteoporos Int.* 2005 Oct 11

### **GENDER DIFFERENCES IN HEALTH HABITS AND IN MOTIVATION FOR A HEALTHY LIFESTYLE AMONG SWEDISH UNIVERSITY STUDENTS.**

The aim of the present study was to investigate gender differences in students' health habits and motivation for a healthy lifestyle. The sample of students comprised a probability systematic stratified sample from each department at a small university in the south-west of Sweden (n = 479). A questionnaire created for this study was used for data collection. Self-rated health was measured by number of health complaints, where good health was defined as having less than three health complaints during the last month. A healthy lifestyle index was computed on habits related to smoking, alcohol consumption, food habits, physical activity and stress. Female students had healthier habits related to alcohol consumption and nutrition but were more stressed. Male students showed a high level of overweight and obesity and were less interested in nutrition advice and health enhancing activities. The gender differences are discussed in relation to the impact of stress on female students' health, and the risk for male students in having unhealthy nutritional habits in combination with being physically inactive and drinking too much alcohol.

*Nurs Health Sci.* 2005 Jun;7(2):107-18

### **REFERENCE VALUES FOR SERUM SILICON IN ADULTS.**

Silicon is an essential nutrient of fundamental importance to human biology. It has been shown that silicon is required for bone, cartilage, and connective tissue formation. However, the assessment of silicon concentration is difficult as reference values are lacking. The aim of the present study was to establish reference values for apparently healthy individuals. Silicon concentrations were determined in serum of 1325 healthy subjects 18-91 years of age using atomic absorption spectrometry. Medians for serum silicon concentrations showed a statistically significant age and sex dependency. In men 18-59 years of age the median was 9.5 micromol/L and decreased to 8.5 micromol/L at 60-74 years of age. In women there was an increase in the median from age 18-29 years (10.00 micromol/L) to 30-44 years (11.10 micromol/L) followed by a decrease in the age group of 45-59 years (9.23 micromol/L). In subjects aged over 74 years the median serum silicon values were 7.70 micromol/L for men and 8.00 micromol/L for women. The most important findings in this study are the decrease of silicon and the course of the silicon concentrations with age, especially in women. The present study is an important prerequisite for studies that aim to identify the health effects and medical implications of silicon.

*Anal Biochem.* 2005 Feb 1;337(1):130-5

**HIGH GLUTATHIONE TURNOVER IN HUMAN CELL LINES REVEALED BY ACIVICIN INHIBITION OF GAMMA-GLUTAMYLTRANSPEPTIDASE AND THE EFFECTS OF THIOL-REACTIVE METALS DURING ACIVICIN INHIBITION.**

**BACKGROUND:** Glutathione is the most abundant nonprotein sulfhydryl-containing compound and constitutes the largest component of the endogenous thiol buffer. Glutathione is known to have multifaceted physiological functions and is a critical factor in protecting organisms against toxicity and disease. Intracellular cysteine concentration is a limiting factor for glutathione synthesis. **METHODS:** In the present study, the metabolism of intra- and extracellular glutathione in HeLa and hepatoma cell cultures is investigated by using different transport inhibitors for cellular uptake of cystine/cysteine. **RESULTS:** There exist several ways of cystine/cysteine transport into HeLa and hepatoma cells, and inhibition of them decreased intracellular concentration of cystine/cysteine and in some cases also of glutathione. It was also shown that a large pool of total cell culture glutathione was located extracellularly in both HeLa and hepatoma cell cultures when gamma-glutamyltranspeptidase (GT) activity was inhibited by acivicin (ACI). Furthermore, the addition of thiol-reactive metal ions significantly increased the total amount of glutathione in hepatoma cell cultures during acivicin inhibition. Thus, occasional determinations of extracellular concentrations of glutathione without GT inhibition strongly underestimate the total turnover of glutathione in a cell culture. **CONCLUSION:** This finding has important implications for future research in glutathione metabolism and the understanding of its role in human health and disease.

*Clin Chim Acta.* 2004 Nov;349(1-2):45-52

**THE MULTIFOOD ALLERGY SYNDROME.**

Multiple food intolerance in infants and young children is increasingly diagnosed. More than 40% of infants less than 1 y.o. could be affected. The syndrome is characterized by the seriousness of atopic dermatitis (SCORAD > 50), by enterocolitis or failure to thrive or various associations of symptoms that may change over time. The evolution is long-lasting. Common food allergens are milk, egg, soy, wheat, but other ones can be implicated. The diagnosis is established by standardized oral challenges. Multiple etiopathogenic factors are involved: atopy, gastro-enteritis induced intestinal hyperpermeability, precocity of food diversification, breast-feeding continued after the onset of symptoms. Amino-acid based formulas have changed the evolution.

*Allerg Immunol (Paris).* 2000 Jan;32(1):12-5

**INTESTINAL PERMEABILITY IN CROHN'S DISEASE PATIENTS AND THEIR FIRST DEGREE RELATIVES.**

**BACKGROUND:** Family studies suggested that an altered intestinal permeability plays a role in the genesis of Crohn's disease. **AIM:** Aim of the present study was to investigate a possible genetic alteration of the mucosal barrier in Crohn's disease. **SUBJECTS:** 16 Crohn's disease patients and 26 of their cohabiting first degree relatives were studied. **METHODS:** To investigate intestinal permeability, Cellobiose/Mannitol test was administered to both groups. **RESULTS:** In the two groups, we found that the median intestinal permeability values were higher and statistically different from those obtained in 32 healthy control subjects as well as in five healthy control families. Six (37.5%) Crohn's disease patients and three (11.5%) of their first degree relatives showed increased individual intestinal permeability values. Intestinal permeability alteration in Crohn's disease patients was unrelated to sex, age, disease activity, localisation, duration, treatment schedule, as well as to serum anti-Saccharomyces cervisiae antibody positivity in a pilot study conducted in 7 Crohn's disease patients; anti-Saccharomyces cervisiae antibody values were negative in all 10 first degree relatives investigated. **CONCLUSIONS:** These findings demonstrate the increase in IP in 37% of the patients and in 11% of their relatives. More extensive investigation of the correlation between ASCA alterations and IP will be needed in both patients with Crohn's disease and their relatives.

*Dig Liver Dis.* 2001 Nov;33(8):680-5

**ALANYL-GLUTAMINE-SUPPLEMENTED PARENTERAL NUTRITION INCREASES LUMINAL MUCUS GEL AND DECREASES PERMEABILITY IN THE RAT SMALL INTESTINE.**

**BACKGROUND:** Effect of supplemental alanyl-glutamine in standard TPN (S-TPN) on luminal mucus gel and small intestinal permeability was investigated. **METHODS:** Thirty Sprague-Dawley rats were divided into group I (n = 10), receiving standard rat

diet; group II (n = 10), receiving S-TPN; and group III (n = 10), receiving alanyl-glutamine-supplemented TPN for 1 week. After 1 week, fluorescein isothiocyanate (FITC)-dextran was injected into the small intestine of the rats, and they were killed. A small intestinal sample and portal blood were obtained for morphologic and functional analysis of mucus gel and intestinal permeability. RESULTS: In group II, thickness and optical density of mucus gel per millimeter serosal length of intestine were significantly lower than group I ( $p < .001$ ) and were significantly higher in group III than in group II ( $p < .001$ ). The number of goblet cells in the villi and in the crypt of the small intestine was significantly lower in group II than in group I ( $p < .001$ ) and was significantly higher in group III than in group II ( $p < .001$ ), with the exception of the villi of jejunum. Villous and crypt surface area per millimeter serosal length of intestine was significantly lower in group II than in group I ( $p < .001$ ) and was significantly higher in group III than in group II ( $p < .001$ ). Small intestinal permeability to FITC-dextran was significantly higher in group II than in group I ( $p < .001$ ) and was significantly lower in group III than in group II ( $p < .001$ ). Glucosamine synthetase level was significantly higher in group III than in group I and ileum of group II ( $p < .001$ ). CONCLUSIONS: Alanyl-glutamine-supplemented TPN prevents a decrease in mucus gel and an increase in small intestinal permeability associated with S-TPN.

*JPEN J Parenter Enteral Nutr.* 1999 Jan-Feb;23(1):24-31

### **NARRATIVE REVIEW: CELIAC DISEASE: UNDERSTANDING A COMPLEX AUTOIMMUNE DISORDER.**

Celiac disease is a common autoimmune disorder that has genetic, environmental, and immunologic components. It is characterized by an immune response to ingested wheat gluten and related proteins of rye and barley that leads to inflammation, villous atrophy, and crypt hyperplasia in the intestine. The disease is closely associated with genes that code for human leukocyte antigens DQ2 and DQ8. Transglutaminase 2 appears to be an important component of the disease, both as a deamidating enzyme that can enhance the immunostimulatory effect of gluten and as a target autoantigen in the immune response. Sensitive and specific serologic tests, including those for anti-transglutaminase antibody, are facilitating fast and noninvasive screening for celiac disease. Thus, they are contributing to a more accurate estimate of the prevalence of the disease and its association with other disorders. Celiac disease is associated with increased rates of anemia, osteoporosis, cancer, neurologic deficits, and additional autoimmune disorders. A gluten-free diet is the mainstay of safe and effective treatment of celiac disease, although its effect on some of the extraintestinal manifestations of the disease remains to be determined.

*Ann Intern Med.* 2005 Feb 15;142(4):289-98

### **WHOLE-BODY PROTEIN METABOLISM ASSESSED BY LEUCINE AND GLUTAMINE KINETICS IN ADULT PATIENTS WITH ACTIVE CELIAC DISEASE.**

To assess the effect of increased renewal of intestinal epithelial cells on leucine and glutamine (Gln) turnover, 4-hour intravenous infusions of L-[1-(13)C]leucine and L-[2-(15)N]Gln were administered to five adult patients with active celiac disease in the postabsorptive state. There was a 35% increase in leucine flux (micromoles per kilogram per hour) in patients (117 +/- 17) compared with healthy controls (96 +/- 11,  $P < .03$ ). Gln flux was increased by 13% in patients (377 +/- 35) versus controls (335 +/- 16,  $P < .04$ ). These results suggest that active celiac disease, characterized by villous atrophy and crypt cell hyperplasia, is associated with a dramatic increase in whole-body protein breakdown as assessed by 13C-leucine, which may contribute per se to the protein malnutrition status of the patients. The increase in Gln utilization as assessed by L-[2-(15)N]Gln was moderate, but may have been offset due to the villose atrophy and ensuing reduced intestinal epithelial cell mass. The results are consistent with the concept that increased renewal of intestinal epithelial cells represents a sizable fraction of whole-body protein turnover and that Gln is an important fuel for epithelial intestinal cells in vivo.

*Metabolism.* 1998 Dec;47(12):1429-33

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