

Treatment of bone loss in oophorectomized women with a combination of ipriflavone and conjugated equine estrogen.

Nozaki M, Hashimoto K, Inoue Y, et al. *Int J Gynaecol Obstet* 1998;62:69-75.

OBJECTIVE: We previously reported that 0.625 mg/day of conjugated equine estrogen (CEE) could not prevent acute bone loss in the first year after oophorectomy. The effect of additional administration of ipriflavone on bone mineral density (BMD) and biochemical indices of bone remodeling were studied to investigate whether concurrent use of CEE and ipriflavone prevent acute bone loss in the early stages following surgical menopause. **METHODS:** One-hundred and sixteen oophorectomized women were randomly divided into four groups according to treatment; group 1: placebo, n = 30; group 2: CEE (0.625 mg/day), n = 29; group 3: ipriflavone (600 mg/day), n = 30; group 4: CEE (0.625 mg/day) plus ipriflavone (600 mg/day), n = 27. Vertebral BMD was measured using dual energy X-ray absorptiometry (DEXA) and two biochemical indices of bone metabolism, urinary pyridinoline (Pyr) and serum intact human osteocalcin (hOC), were also measured before, 24 weeks, and 48 weeks after initiation of treatment. **RESULTS:** BMD was reduced 48 weeks after treatment by 6.1, 3.9 and 5.1% in groups 1-3, respectively, but by only 1.2% in group 4. Pyr decreased by 49.5, 32.0 and 41.5% in groups 2-4, respectively. hOC also decreased by 45.2 and 21.6% in groups 2 and 4, but increased by 40.5% in group 3, suggesting an inhibitory action of CEE and ipriflavone on the turnover of bone metabolism and stimulatory action of ipriflavone on bone formation. **CONCLUSION:** Concomitant use of ipriflavone with CEE from an early stage after oophorectomy inhibited bone loss and was considered to be effective in maintaining bone mass after oophorectomy.

Effect of ipriflavone—a synthetic derivative of natural isoflavones—on bone mass loss in the early years after menopause.

Gennari C, Agnusdei D, Crepaldi G, et al.
Menopause 1998;5:9-15.

OBJECTIVE: We studied whether oral administration of ipriflavone, a synthetic derivative of naturally occurring isoflavones, could prevent bone loss occurring shortly after menopause. **DESIGN:** Fifty-six women with low vertebral bone density and with postmenopausal age less than five years were randomly allocated to receive either ipriflavone, 200 mg three times daily, or placebo. All subjects also received 1,000 mg elemental calcium daily. **RESULTS:** Vertebral bone density declined after two years in women taking only calcium (4.9 +/- 1.1%, SEM, $p = 0.001$), but it did not change in those receiving ipriflavone (-0.4 +/- 1.1%, n.s.). A significant ($p = 0.010$) between-treatment difference was evidenced at both year 1 and year 2. At the end of the study, urine hydroxyproline/creatinine excretion was higher in the control group than in the ipriflavone group, as compared to no difference at baseline. Five patients taking ipriflavone and five taking placebo experienced gastrointestinal discomfort or other adverse reactions, but only one and four subjects, respectively, had to discontinue the study. **CONCLUSIONS:** Ipriflavone prevents the rapid bone loss following early menopause. This effect is associated with a reduction of bone turnover rate.

Ethnoveterinary medicines used for ruminants in Trinidad and Tobago.

Lans C, Brown G. *Prev Vet Med* 1998;35:149-163.

Ethnoveterinary research was conducted in Trinidad and Tobago in 1995, in order to document existing ethnoveterinary practices. This paper describes 20 medicinal plants used to treat ruminants. The main plants used were *Azadirachta indica* and *Curcuma longa*. Medicinal plants were used predominantly for endoparasites, internal and external injuries and pregnancy-related conditions. A 4-stage process was used to conduct the research and document the ethnoveterinary practices. This documentation could provide a foundation for the further scientific study and verification of those practices which merit such study.

Abstracts

Recently Published Abstracts

Effects of combined low dose of the isoflavone derivative ipriflavone and estrogen replacement on bone mineral density and metabolism in postmenopausal women.

Gambacciani M, Ciaponi M, Cappagli B, et al. *Maturitas* 1997;28:75-81.

OBJECTIVES: To assess the pattern of biochemical markers of bone metabolism and vertebral bone mineral density in early postmenopausal women treated with combined ipriflavone and low dose conjugated estrogens. **METHODS:** Bone biochemical markers and vertebral bone density were evaluated in a longitudinal, comparative, 2 year study conducted in postmenopausal women treated with sole calcium supplementation (500 mg/day), or with either ipriflavone (IP) at the standard dose (600 mg/day) plus the same calcium dose, low dose conjugated estrogens (CE) (0.3 mg/day) plus calcium, or low dose IP (400 mg/day) plus low dose CE (0.3 mg/day) plus calcium. The results were analyzed by repeated measures analysis of variance, as appropriate. **RESULTS:** No modifications of both urinary excretion of hydroxyproline and plasma osteocalcin levels were observed in calcium and in CE-treated women, while vertebral bone density significantly decreased ($P < 0.0001$) in both groups. In IP or IP + CE-treated women, plasma osteocalcin did not show any modification, while urinary hydroxyproline showed a significant ($P < 0.05$) decrease, that paralleled a significant ($P < 0.05$) increase in vertebral bone density. **CONCLUSION:** Postmenopausal IP administration, at the standard dose of 600 mg/day, can prevent the increase in bone turnover and the decrease in bone density that follow ovarian failure. The same effect can be obtained with the combined administration of low dose (400 mg/day) IP with low dose (0.3 mg/day) CE.

Pharmacological nutrition after burn injury.

De-Souza DA, Greene LJ.
J Nutr 1998;128:797-803.

Burn patients develop pathophysiological alterations, which include extensive nitrogen loss, malnutrition, markedly increased metabolic rate and immunologic deficiency. This predisposes burn patients to frequent infections, poor wound healing, increased length of hospitalization and increased mortality. The nutritional support requires high protein and high energy diets preferably administered enterally soon after injury. The effects of increased dietary components such as glutamine, arginine and (n-3) fatty acids and related compounds have been evaluated in burn victims. These components, when supplied in quantities two to seven times of those in normal diets of healthy persons, appear to have beneficial pharmacological effects on the pathophysiological alterations associated with burns. However, the efficacy of immune-enhancing diets remains to be convincingly shown.

The neuroprotective drug vinpocetine prevents veratridine-induced $[Na^+]_i$ and $[Ca^{2+}]_i$ rise in synaptosomes.

Tretter L, Adam-Vizi V.
Neuroreport 1998;9:1849-1853.

The effect of the neuroprotective drug, vinpocetine on the veratridine-evoked $[Na^+]_i$ and $[Ca^{2+}]_i$ rise in isolated nerve terminals was studied. Vinpocetine, in a pharmacologically relevant concentration range (0.4-10 μM) reduced the increase of $[Na^+]_i$ induced by veratridine (100 μM). The effect of the drug was concentration-dependent with 10 μM vinpocetine completely preventing the increase of $[Na^+]_i$. The $[Ca^{2+}]_i$ rise in response to veratridine was also prevented by vinpocetine. In addition, the $[Ca^{2+}]_i$ signal induced by depolarization with 20 mM K^+ was reduced by vinpocetine (1-20 μM). This effect was not influenced by preincubation with 1 μM TTX and was also observed when Na^+ was replaced by N-methyl glucamine in the medium. It is concluded that vinpocetine is capable of inhibiting voltage-dependent Na^+ and Ca^{2+} channels, respectively, and these effects might contribute to the neuroprotection exerted by the drug.

Abstracts

Recently Published Abstracts

Genetic disorders of carnitine metabolism and their nutritional management.

Kerner J, Hoppel C. *Annu Rev Nutr* 1998;18:179-206.

Carnitine functions as a substrate for a family of enzymes, carnitine acyltransferases, involved in acyl-coenzyme A metabolism and as a carrier for long-chain fatty acids into mitochondria. Carnitine biosynthesis and/or dietary carnitine fulfill the body's requirement for carnitine. To date, a genetic disorder of carnitine biosynthesis has not been described. A genetic defect in the high-affinity plasma membrane carnitine-carrierin leads to renal carnitine wasting and primary carnitine deficiency. Myopathic carnitine deficiency could be due to an increase in efflux moderated by the carnitine-carrierout. Defects in the carnitine transport system for fatty acids in mitochondria have been described and are being examined at the molecular and pathophysiological levels. The nutritional management of these disorders includes a high-carbohydrate, low-fat diet and avoidance of those events that promote fatty acid oxidation, such as fasting, prolonged exercise, and cold. Large-dose carnitine treatment is effective in systemic carnitine deficiency.

Ephedrine-activated physiological sexual arousal in women.

Meston CM, Heiman JR. *Arch Gen Psychiatry* 1998;55:652-656.

BACKGROUND: The present investigation was designed to provide the first empirical examination of the effects of ephedrine sulfate, an alpha- and beta-adrenergic agonist, on subjective and physiological sexual arousal in women. The purpose was to help elucidate the effects of increased peripheral adrenergic activity on sexual response in women. **METHODS:** Twenty sexually functional women participated in 2 experimental conditions in which subjective (self-report) and physiological (vaginal photoplethysmography) sexual responses to erotic stimuli were measured following administration of either ephedrine sulfate (50 mg) or placebo in a randomized, double-blind, cross-over protocol. **RESULTS:** Ephedrine significantly ($P < .01$) increased vaginal pulse amplitude responses to the erotic films and had no significant ($P > .10$) effect on subjective ratings of sexual arousal. **CONCLUSIONS:** Ephedrine can significantly facilitate the initial stages of physiological sexual arousal in women. These findings have implications for deriving new pharmacological approaches to the management of sexual dysfunction in women.

Quality of life during and between hemodialysis treatments: role of L-carnitine supplementation.

Sloan RS, Kastan B, Rice SI, et al. *Am J Kidney Dis* 1998;32:265-272.

End-stage renal disease affects every aspect of a patient's life, including perception of health and quality of life. It is likely that a hemodialysis patient's perceptions of health-related quality of life directly influence compliance with medical, nursing, and nutritional prescriptions. Because L-carnitine supplementation is known to enhance muscle strength and energy in hemodialysis patients, we hypothesized that L-carnitine supplementation would enhance a hemodialysis patient's perception of health-related quality of life. To test this hypothesis, 1 g L-carnitine or placebo was administered orally to 101 patients immediately before and after every hemodialysis treatment for 6 months. To assess health-related quality of life from the patient's perspective, the Medical Outcomes Study Short Form 36 instrument was administered before the study and at 1.5-month intervals for the duration of the study. In addition, a 10-item questionnaire designed to assess common intradialytic symptoms was administered at the end of each dialysis treatment. Other parameters analyzed included Kt/V(urea) and level of nutrition. In the 6-month group, oral L-carnitine supplementation had an early positive effect on general health ($P < 0.02$) and physical function ($P < 0.03$), but the perceived effect was not sustained throughout the 6 months of the study. In the 3-month group, L-carnitine supplementation improved vitality ($P < 0.02$) and general health ($P < 0.01$). There was no association between Kt/V(urea) and perceived health-related quality of life. Serum albumin concentration was directly correlated to how patients perceived the quality of their lives.

Prevention of hyperlipidemic acute pancreatitis during pregnancy with medium-chain triglyceride nutritional support.

Mizushima T, Ochi K, Matsumura N, et al. *Int J Pancreatol* 1998;23:187-192.

BACKGROUND: Prevention and therapy of gestational hyperlipidemic pancreatitis are fetal morbidity and mortality. **RESULTS:** We describe a 32-yr-old female with lipoprotein lipase-deficient familial hypertriglyceridemia who had recurrent episodes of acute pancreatitis. The third episode occurred with worsened hyperlipidemia 7 yr earlier at 32 wk of her first pregnancy and resulted in fetal death. The fourth and fifth episodes were also accompanied by marked hyperlipidemia probably caused by drug discontinuance and dietary noncompliance. She became pregnant. Serum triglyceride levels were controlled below 2000 mg/dL by strict monitoring with low-fat, low-calorie diet and MCT nutritional support. A premature but healthy infant was born by Cesarean delivery at 36 wk of gestation when the mother presented with mild abdominal pain and was found to have uterine contractions. The ensuing clinical course has been uneventful. **CONCLUSION:** A combination of diet therapy, nutritional support with medium-chain triglycerides (MCT), and well-planned preterm Cesarean delivery on demand is an effective measure to prevent gestational hyperlipidemic pancreatitis and leads to successful childbirth

Cytotoxicity of endodontic materials.

Osorio RM, Hefti A, Vertucci FJ, Shawley AL. *J Endod* 1998;24:91-96.

An in vitro cell culture model of human gingival fibroblasts and L-929 cells was used to measure the cytotoxicity of currently used root canal sealers Endomet, CRCS, and AH26 and root-end filling materials Amalgam, Gallium GF2, Ketac Silver, mineral trioxide aggregate (MTA), and Super-EBA. Cytotoxic effects were assessed using the MTT assay for mitochondrial enzyme activity and the CV assay for cell numbers. Using inserts culture and L-929 fibroblasts. All-Bond-2 was also evaluated. The statistical analysis of results showed that CRCS was the least cytotoxic sealer followed by Endomet and AH26. Among root-end filling materials, MTA was not cytotoxic; Gallium GF2 displayed little cytotoxicity; and Ketac Silver, Super-EBA, and Amalgam showed higher levels of cytotoxicity. All Bond-2 also displayed a high degree of cytotoxicity. CRCS was the best root canal sealer and MTA the best root-end filling material. The outcome was favorable also for Gallium GF2 as a retrofilling material.

Medium chain fatty acid metabolism and energy expenditure: obesity treatment implications.

Papamandjaris AA,
MacDougall DE, Jones PJ.
Life Sci 1998;62:1203-1215.

Fatty acids undergo different metabolic fates depending on their chain length and degree of saturation. The purpose of this review is to examine the metabolic handling of medium chain fatty acids (MCFA) with specific reference to intermediary metabolism and postprandial and total energy expenditure. The metabolic discrimination between varying fatty acids begins in the GI tract, with MCFA being absorbed more efficiently than long chain fatty acids (LCFA). Subsequently, MCFA are transported in the portal blood directly to the liver, unlike LCFA which are incorporated into chylomicrons and transported through lymph. These structure based differences continue through the processes of fat utilization; MCFA enter the mitochondria independently of the carnitine transport system and undergo preferential oxidation. Variations in ketogenic and lipogenic capacity also exist. Such metabolic discrimination is supported by data in animals and humans showing increases in postprandial energy expenditure after short term feeding with MCFA. In long term MCFA feeding in animals, weight accretion has been attenuated. These differences in metabolic handling of MCFA versus LCFA are considered with the conclusion that MCFA hold potential as weight loss agents.

Haematological effects of oral cobalamin preparations on patients with megaloblastic anaemia.

Kondo H. *Acta Haematol*
1998;99:200-205.

We investigated the haematological effects of a massive dose of oral cobalamin (vitamin B12) on patients with cobalamin deficiency anaemia who had severe anaemia with a few neurological impairments and found that oral treatment was almost as effective as conventional injection therapy. The recovery of haematological indices with oral cobalamin preparations was slightly slower than with parenteral preparations, although the subjective symptoms disappeared soon after the start of therapy. The results of this study indicate that oral treatment keeps the cobalamin body stores satisfactorily filled and might be useful for older patients in whom injecting might be difficult.

Function of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia and low back pain.

Griep EN, Boersma JW, Lentjes EG, et al. *J Rheumatol* 1998;25:1374-1381.

OBJECTIVE: We suggested fibromyalgia (FM) is a disorder associated with an altered functioning of the stress-response system. This was concluded from hyperreactive pituitary adrenocorticotrophic hormone (ACTH) release in response to corticotropin-releasing hormone (CRH) and to insulin induced hypoglycemia in patients with FM. In this study, we tested the validity and specificity of this observation compared to another painful condition, low back pain. **METHODS:** We recruited 40 patients with primary FM (F:M 36:4), 28 patients (25:3) with chronic noninflammatory low back pain (LBP), and 14 (12:2) healthy, sedentary controls. A standard 100 microg CRH challenge test was performed with measurement of ACTH and cortisol levels at 9 time points. They were also subjected to an overnight dexamethasone suppression test, followed by injection of synthetic ACTH1-24. At 9 AM, the patients divided in 2 groups, received either 0.025 or 0.100 microg ACTH/kg body weight to test for adrenocortical sensitivity. Basal adrenocortical function was assessed mainly by measurement of 24 h urinary excretion of free cortisol. **RESULTS:** Compared to the controls, the patients with FM displayed a hyperreactive ACTH release in response to CRH challenge (ANOVA interaction effect $p = 0.001$). The mean ACTH response of the patients with low back pain appeared enhanced also, but to a significantly lesser extent ($p = 0.02$ at maximum level) than observed in the patients with FM. The cortisol response was the same in the 3 groups. Following dexamethasone intake there were 2 and 4 nonsuppressors in the FM and LBP groups, respectively. The very low and low dose of exogenous ACTH1-24 evoked a dose and time dependent cortisol response, which, however, was not significantly different between the 3 groups. The 24 h urinary free cortisol levels were significantly lower ($p = 0.02$) than controls in both patient groups; patients with FM also displayed significantly lower ($p < 0.05$) basal total plasma cortisol than controls. **CONCLUSION:** The present data validate and substantiate our preliminary evidence for a dysregulation of the HPA axis in patients with FM, marked by mild hypocortisolemia, hyperreactivity of pituitary ACTH release to CRH, and glucocorticoid feedback resistance. Patients with LBP also display hypocortisolemia, but only a tendency toward the disrupted HPA features observed in the patients with FM. We propose that a reduced containment of the stress-response system by corticosteroid hormones is associated with the symptoms of FM.

Pain treatment of fibromyalgia by acupuncture.

Sprott H, Franke S, Kluge H, Hein G. *Rheumatol Int* 1998;18:35-36.

The lack of objective parameters makes the measurement of pain and the efficacy of pain treatment in patients with chronic pain very difficult. We performed acupuncture therapy in fibromyalgia patients and established a combination of methods to objectify pain measurement before and after therapy. The parameters corresponded to patients' self-report. Twenty-nine fibromyalgia patients as defined by ACR-criteria (25 women, 4 men) with a mean age of 48.2 +/- 2.0 years and a mean disease duration of 6.1 +/- 1.0 years participated in the study. Pain levels and positive tender points were assessed using the visual analogue scale (VAS, i.e., range 0-100 mm) and dolorimetry. Serotonin and substance P levels in serum and the serotonin concentration in platelets were measured concomitantly. During acupuncture therapy no analgesic medication was allowed. The VAS scores decreased from 64.0 +/- 3.4 mm before therapy to 34.5 +/- 4.3 mm after therapy ($P < 0.001$). Dolorimetry revealed a decreased number of tender points after therapy from 16.0 +/- 0.6 to 11.8 +/- 1.0, $P < 0.01$. Serotonin levels decreased from 715.8 +/- 225.8 micrograms/10(12) platelets to 352.4 +/- 47.9 micrograms/10(12) platelets ($P < 0.01$), whereas the serum concentration increased from 134.0 +/- 14.3 ng/ml to 171.2 +/- 14.6 ng/ml ($P < 0.01$). Substance P levels in serum increased from 43.4 +/- 3.5 pg/ml to 66.9 +/- 8.8 pg/ml ($P < 0.01$). Acupuncture treatment of patients with fibromyalgia was associated with decreased pain levels and fewer positive tender points as measured by VAS and dolorimetry. This was accompanied by decreased serotonin concentration in platelets and an increase of serotonin and substance P levels in serum. These results suggest that acupuncture therapy is associated with changes in the concentrations of pain-modulating substances in serum. The preliminary results are objective parameters for acupuncture efficacy in patients with fibromyalgia.

Abstracts

Recently Published Abstracts

Zinc supplementation improves glucose disposal in patients with cirrhosis.

Marchesini G, Bugianesi E, Ronchi M, et al. *Metabolism* 1998;47:792-798.

Zinc deficiency is common in cirrhosis, and was proved to affect nitrogen metabolism. In experimental animals, zinc status may also affect glucose disposal, and acute zinc supplementation improves glucose tolerance in healthy subjects. This study was aimed at measuring the effects of long-term oral zinc supplements on glucose tolerance in cirrhosis. The time courses of glucose, insulin, and C-peptide in response to an intravenous (i.v.) glucose load were analyzed by the minimal-model technique before and after long-term oral zinc supplements (200 mg three times per day for 60 days) in 10 subjects with advanced cirrhosis and impaired glucose tolerance or diabetes. The test was performed using a simplified procedure, based on 20 blood samples collected within 4 hours from the glucose load. Normal values were obtained in 25 age-matched healthy subjects. Zinc levels were low to normal or reduced before treatment, and were normalized by oral zinc. Glucose disappearance improved by greater than 30% in response to treatment. There were no changes in pancreatic insulin secretion and systemic delivery, or in the hepatic extraction of insulin. Insulin sensitivity (SI), which was reduced by 80% before treatment, did not change. Glucose effectiveness (SG) was nearly halved in cirrhosis before treatment (0.013 [SD 0.007] min⁻¹) v. 0.028 [SD 0.009] in controls; $P < .001$, and increased to 0.017 (SD 0.009) after zinc ($P < .05$ v. baseline). The return to normal of plasma zinc levels after long-term zinc treatment in advanced cirrhosis improves glucose tolerance via an increase of the effects of glucose per se on glucose metabolism. Poor zinc status may contribute to the impaired glucose tolerance and diabetes of cirrhosis.

Effect of chronic administration of Ginkgo biloba extract or Ginkgolide on the hypothalamic-pituitary-adrenal axis in the rat.

Marcilhac A, Dakine N, Bourhim N, et al. *Life Sci* 1998;62:2329-2340.

The hypersecretion of glucocorticoids during exposure to various stressors may induce or worsen pathological states in predisposed subjects. Therefore it is of interest to evaluate drugs able to reduce glucocorticoid secretion. It has recently been shown that chronic administration of a Ginkgo biloba extract (EGb 761) inhibits stress-induced corticosterone hypersecretion through a reduction in the number of adrenal peripheral benzodiazepine receptors. The present study was designed to analyze the effect of EGb 761 and one of its components, Ginkgolide B on the biosynthesis and secretion of CRH and AVP, the hypothalamic neurohormones that regulate the pituitary-adrenal axis. Chronic administration of EGb 761 (50 or 100 mg/kg p.o. daily for 14 days) reduced basal corticosterone secretion and the subsequent increase in CRH and AVP gene expression. Under the same conditions, surgically-induced increase in CRH secretion was attenuated while the activation of CRH gene expression, ACTH and corticosterone secretion following insulin-induced hypoglycemia remained unchanged. Chronic i.p. injection of Ginkgolide B reduced basal corticosterone secretion without alteration in the subsequent CRH and AVP increase. However, the stimulation of CRH gene expression by insulin-induced hypoglycemia was attenuated by Ginkgolide B. These data confirm that the administration of EGb 761 and Ginkgolide B reduces corticosterone secretion. In addition, these substances act also at the hypothalamic level and are able to reduce CRH expression and secretion. However the latter effect appears to be complex and may depend upon both the nature of stress and substance (Ginkgolide B or other compounds of EGb 761).

Abstracts

Recently Published Abstracts

Dehydroepiandrosterone decreases serum tumor necrosis factor-alpha and restores insulin sensitivity: independent effect from secondary weight reduction in genetically obese Zucker fatty rats.

Kimura M, Tanaka S, Yamada Y, et al.

Endocrinology

1998;139:3249-3253.

Dehydroepiandrosterone (DHEA) and its sulfate ester are the most abundant circulating adrenal steroids in humans. Administration of DHEA has been reported to have beneficial effects on obesity, hyperlipidemia, diabetes, and atherosclerosis in obese rodents, although its effects on insulin resistance have not been fully elucidated. In this study, the effects of DHEA treatment on insulin sensitivity were investigated in genetically obese Zucker rats, an animal model of insulin resistance, using the euglycemic clamp technique. After 0.4% DHEA was administered for 10 days to female obese Zucker rats aged 16 weeks, body weight and plasma insulin decreased and glucose disposal rate (GDR), which was normally reduced in obese rats, rose significantly compared with age- and sex-matched control obese rats. On the other hand, although the pair-fed obese rats also showed levels of weight reduction similar to those of DHEA-treated rats, the increase in GDR of DHEA-treated rats was significantly greater than in pair-fed rats, suggesting a direct ameliorating effect of DHEA on insulin sensitivity of obese rats. Serum concentration of tumor necrosis factor (TNF)-alpha, one of cytokines causing insulin resistance, was also reduced significantly in DHEA-treated, but not in pair-fed obese rats. In conclusion, our results suggest that DHEA treatment reduces body weight and serum TNF-alpha independently, and that both may ameliorate insulin resistance in obese Zucker fatty rats.

Mechanisms of cancer inhibition by anti-oxidant nutrients.

Shklar G. *Oral Oncol*
1998;34:24-29.

The cancer inhibitory properties of anti-oxidant micronutrients have been well established in experimental animal models and cell culture studies. Human studies have also tended to indicate an inhibition of various forms of cancer and the regression of some precancerous lesions. The biological mechanisms for cancer inhibition and regression are now gradually becoming understood, and the anti-oxidant nutrients appear to act through a number of pathways common to most of the agents studied. These various micronutrients appear to act through a complex group of “common pathways” of anticancer activity based upon three major mechanisms: (1) tumor inhibition by immune cytokines; (2) stimulation of cancer suppressor genes, such as “wild type” p53, and diminished expression or dysregulation of oncogenes such as mutant p53 and H-ras; (3) inhibition of tumor angiogenesis through the inhibition of angiogenesis-stimulating factors such as TGF alpha. Retinoid action differs, in some respects, from other micronutrient anticancer mechanisms and appears to relate to its stimulation of cellular differentiation and resultant apoptosis of neoplastic cells. Combinations of anti-oxidant nutrients have been shown to be synergistic in their anticancer activity, probably due to their optimal anticancer activity at different oxygen potentials. Selectivity in the action on cancer cells, as opposed to normal cells, is a major feature of the anti-oxidant micronutrients.

Abstracts

Recently Published Abstracts

Dietary and supplemental calcium and the recurrence of colorectal adenomas.

Hyman J, Baron JA, Dain BJ, et al. *Cancer Epidemiol Biomarkers Prev* 1998;7:291-295.

The association between calcium intake and the risk of colorectal neoplasia remains controversial. This analysis prospectively investigated the association between dietary and supplemental calcium intake and recurrent colorectal adenomas. Participants were part of a multicenter, randomized clinical trial of antioxidant vitamins. The study endpoints were adenomas detected between surveillance colonoscopies conducted at approximately 1 year and 4 years after study entry. Baseline intake of energy-adjusted calcium derived from a food frequency questionnaire was used as the main exposure of interest. Calcium supplement use was assessed by semiannual questionnaires. Logistic regression was used to compute odds ratios and 95% confidence limits, and Poisson regression was used to estimate rate ratios. Subjects in the fifth quintile of dietary calcium had an adjusted odds ratio of 0.72 (95% confidence interval, 0.43-1.22) compared to those in the lowest quintile. Investigation of the numbers of adenomas yielded stronger findings: the rate ratio for the fifth quintile versus the first was 0.63 (95% confidence interval, 0.39-1.02). Dietary calcium seemed to have a greater effect among individuals with a high-fat diet than among those with a low-fat diet; however, the interaction was not statistically significant. Use of calcium supplements was not related to adenoma recurrence. These results suggest that a high calcium intake may be associated with a reduction in risk of recurrent adenomas, especially among individuals on a high-fat diet.

Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis.

Qiu GX, Gao SN, Giacobelli G, et al.

Arzneimittelforschung
1998;48:469-474.

A double-blind therapeutic investigation was performed on 178 Chinese patients suffering from osteoarthritis of the knee randomized into two groups, one treated for 4 weeks with glucosamine sulfate (GS, CAS 29031-19-4, Viartiril-S) at the daily dose of 1,500 mg and the other with ibuprofen (IBU, CAS 15687-27-1) at the daily dose of 1,200 mg. Knee pain at rest, at movement and at pressure, knee swelling, improvement and therapeutic utility as well as adverse events and drop-outs were recorded after 2 and 4 weeks of treatment. The variables were recorded also after 2 weeks of treatment discontinuation in order to appreciate the remnant therapeutic effect. Both GS and IBU significantly reduced the symptoms of osteoarthritis with the trend of GS to be more effective. After 2 weeks of drug discontinuation there was a remnant therapeutic effect in both groups, with the trend to be more pronounced in the GS group. GS was significantly better tolerated than IBU, as shown by the adverse drug reactions (6% in the patients of the GS group and 16% in the IBU group— $p = 0.02$) and by the drug-related drop-outs (0% of the patients in the GS group and 10% in the IBU group— $p = 0.0017$). The better tolerability of GS is explained by its mode of action, because GS specifically curbs the pathogenic mechanisms of osteoarthritis and does not inhibit the cyclo-oxygenases as the non-steroidal anti-inflammatory drugs (NSAIDs) do, with the consequent anti-inflammatory analgesic activities but also with the several adverse reactions due to this not targeted effect. The present study confirms that GS is a selective drug for osteoarthritis, as effective on the symptoms of the disease as NSAIDs but significantly better tolerated. For these properties GS seems particularly indicated in the long-term treatments needed in osteoarthritis.

Abstracts

Recently Published Abstracts

A double-blind, placebo-controlled pilot study of glutamine therapy for abnormal intestinal permeability in patients with AIDS.

Noyer CM, Simon D, Borczuk A, et al. *Am J Gastroenterol* 1998;93:972-975.

OBJECTIVES: Up to 20% of patients with AIDS have abnormal intestinal permeability (IP). Glutamine seems to play an important role in preventing the increase in IP and loss of intestinal mucosal mass associated with total parenteral nutrition, and may be superior to glucose for oral rehydration in the setting of intestinal infection. This study was designed to see if supplemental glutamine could alter the abnormal IP of AIDS. **METHODS:** Randomly chosen patients with AIDS from the Jacobi Medical Center human immunodeficiency virus (HIV) clinic underwent IP testing using lactulose and mannitol. Those with abnormal IP were enrolled. Duodenal biopsies were performed with a Crosby capsule and the patients were randomized in a double-blind fashion to receive placebo or glutamine (4 g/day or 8 g/day) for 28 days, after which intestinal permeability tests and duodenal biopsies were repeated. Intestinal morphology was graded by ratio of villus height to crypt depth, and by degree of inflammation. **RESULTS:** All patients complied with the therapy and there were no dropouts or reported side effects. The results showed less worsening of IP with the 4 g/day dose, compared with placebo. At the 8 g/day dose, there was stabilization of IP and improved absorption of mannitol. Intestinal morphology and inflammation did not change in any group. **CONCLUSIONS:** These results, although not significant, suggest a trend towards improved IP and enhanced intestinal absorption with glutamine. Glutamine doses of at least 20 g/day may be necessary to improve IP. We recommend further studies at higher doses and for longer durations.

Melatonin as a new possible anti-inflammatory agent.

Lissoni P, Rovelli F, Meregalli S, et al. *J Biol Regul Homeost Agents* 1997;11:157-159.

Several experiments have suggested that the pineal hormone melatonin (MLT) may regulate cancer growth by exerting both oncostatic and immunomodulating effects. In particular, MLT would stimulate the anticancer immunity induced by interleukin-2 (IL-2). Recent studies seem to suggest that the activation of the inflammatory response may counteract the anticancer efficacy of IL-2 immunotherapy because of the immunosuppressive action of inflammatory-related cytokines, mainly IL-6. At present, it is still unknown whether MLT may influence host immune antitumor defences by modulating the inflammatory response. To analyze this hypothesis, we have evaluated the effects of a chronic administration of MLT on some of the commonly used markers of inflammation, including erythrocyte sedimentation rate (ESR), IL-6, neopterin and SIL-2R, in patients with evidence of activation of the inflammatory response due to advanced solid neoplasms or auto-immune diseases. The study included 14 patients (solid tumors: 9; autoimmune diseases: 5). MLT was given orally at 20 mg/day during the dark phase of the day for 7 consecutive days. Mean serum levels of IL-6, neopterin and SIL-2R significantly decreased in both groups of patients. ESR values also decreased on therapy, without, however, significant differences. This preliminary study shows that the pineal hormone MLT may inhibit the acute inflammatory reaction. Therefore, because of the immunosuppressive action of inflammation-related cytokines, this study could suggest that MLT may contribute to the generation of the immune reaction against cancer at least in part by removing the immunosuppression related to the activation of the inflammatory response.

Abstracts

Recently Published Abstracts

Retardation of experimental tumorigenesis and reduction in DNA adducts by turmeric and curcumin.

Krishnaswamy K, Goud VK, Sesikeran B, et al. *Nutr Cancer* 1998;30:163-166.

Turmeric and its active principle curcumin have been extensively investigated for their antimutagenic and antioxidant effects in bacterial and animal systems. Because oral cancers are common in India, an experimental model of 7,12-dimethylbenzanthracene-induced buccal pouch tumors in Syrian Golden hamsters was used to evaluate the tumor retardation effects of turmeric and curcumin. Turmeric and/or curcumin was administered in the diet and/or applied locally for 14 weeks along with 7,12-dimethylbenzanthracene. After the experimental period, the animals were sacrificed and oral pouches were examined for tumor number and size. DNA adducts were estimated by ³²P postlabel assay in the cheek pouches. Neoplastic changes were graded by histopathology. The results of the study suggest that turmeric or curcumin in the diet and/or applied locally significantly reduced DNA adducts at the target site. Tumor number and tumor burden were significantly lower ($p < 0.05$) in the animals that received turmeric in the diet and applied locally. The histopathological examinations suggested that the neoplastic grading was least in the animals fed or painted with curcumin ($p < 0.05$). The current study demonstrates that turmeric or curcumin administered in the diet or applied as paint may have a plausible chemopreventive effect on oral precancerous lesions.

Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients.

Edwards R, Peet M, Shay J, Horrobin D. *J Affect Disord* 1998;48:149-155.

BACKGROUND: There is a hypothesis that lack of n-3 polyunsaturated fatty acids (PUFAs) is of aetiological importance in depression. Docosahexaenoic acid, a member of the n-3 PUFA family, is a crucial component of synaptic cell membranes. The aim of this study was to measure RBC membrane fatty acids in a group of depressed patients relative to a well matched healthy control group. **METHOD:** Red blood cell (RBC) membrane levels, and dietary PUFA intake were measured in 10 depressed patients and 14 matched healthy control subjects. **RESULTS:** There was a significant depletion of RBC membrane n-3 PUFAs in the depressed subjects which was not due to reduced calorie intake. Severity of depression correlated negatively with RBC membrane levels and with dietary intake of n-3 PUFAs. **CONCLUSION:** Lower RBC membrane n-3 PUFAs are associated with the severity of depression. **LIMITATIONS:** Although patient numbers were small, confounding factors were well controlled for and the results were highly significant. Results of the dietary data would tend to be weakened due to the limitations associated with dietary assessment. **CLINICAL RELEVANCE:** The findings raise the possibility that depressive symptoms may be alleviated by n-3 PUFA supplementation.

Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression.

Arlt W, Justl HG, Callies F, et al. *J Clin Endocrinol Metab* 1998;83:1928-1934.

Women with adrenal insufficiency suffer from chronic dehydroepiandrosterone (sulfate) [DHEA(S)] deficiency. To define a suitable dose for DHEA replacement, we studied the pharmacokinetics and biotransformation of orally administered DHEA in nine healthy female volunteers (mean age 23.3 +/- 4.1 yr, mean body mass index 22.5 +/- 1.8 kg/m²) with transient suppression of adrenal androgen secretion because of dexamethasone (dex) administration (4 x 0.5 mg/day for 4 days). Diurnal blood sampling was performed during the early follicular phase of four subsequent menstrual cycles (study period 1: baseline; study periods 2-4: dex + placebo, dex + 50 mg DHEA or dex + 100 mg DHEA in a randomized cross-over design). Dex induced not only a significant suppression of serum cortisol (to 8% of baseline) but also of DHEA (18%), DHEA(S) (16%), and androstenedione (26%), as well as of testosterone (28%), dihydrotestosterone (43%), and estrone (54%). Oral administration of 50 mg DHEA led to restoration of DHEA(S) baseline levels, whereas 100 mg induced supraphysiological concentrations [baseline vs. 50 mg DHEA vs. 100 mg DHEA: area under the concentration-time curve (AUC) 0-12 h DHEA: 280 +/- 85 vs. 241 +/- 73 vs. 383 +/- 106 nmol/L x h; AUC 0-12 h DHEA(S): 89.1 +/- 48.4 vs. 139.6 +/- 43.5 vs. 213.3 +/- 21.6 nmol/L x h). Serum concentrations of dihydrotestosterone and estrone were restored to baseline after 50 mg DHEA, whereas baseline testosterone and androstenedione levels were only achieved by administration of 100 mg DHEA. In conclusion, 50 mg DHEA seems to be a suitable replacement dose in females with adrenal insufficiency. Furthermore, the rapid and lasting conversion to potent androgens demonstrates a potential role of DHEA for androgen replacement in females in general.

Effects of flavonoids and vitamin C on oxidative DNA damage to human lymphocytes.

Noroozi M, Angerson WJ, Lean ME. *Am J Clin Nutr* 1998;67:1210-1218.

This study assessed the antioxidant potencies of several widespread dietary flavonoids across a range of concentrations and compared with vitamin C as a positive control. The antioxidant effects of pretreatment with flavonoids and vitamin C, at standardized concentrations (7.6, 23.2, 93, and 279.4 micromol/L), on oxygen radical-generated DNA damage from hydrogen peroxide (100 micromol/L) in human lymphocytes were examined by using the single-cell gel electrophoresis assay (comet assay). Pretreatment with all flavonoids and vitamin C produced dose-dependent reductions in oxidative DNA damage. At a concentration of 279 micromol/L, they were ranked in decreasing order of potency as follows: luteolin (9% of damage from unopposed hydrogen peroxide), myricetin (10%), quercetin (22%), kaempferol (32%), quercitrin (quercetin-3-L-rhamnoside) (45%), apigenin (59%), quercetin-3-glucoside (62%), rutin (quercetin-3-beta-D-rutinoside) (82%), and vitamin C (78%). The protective effect of vitamin C against DNA damage at this concentration was significantly less than that of all the flavonoids except apigenin, quercetin-3-glucoside, and rutin. The ranking was similar with estimated ED50 (concentration to produce 50% protection) values. The protective effect of quercetin and vitamin C at a concentration of 23.2 micromol/L was found to be additive (quercetin: 71% of maximal DNA damage from unopposed hydrogen peroxide; vitamin C: 83%; both in combination: 62%). These data suggest that the free flavonoids are more protective than the conjugated flavonoids (eg, quercetin compared with its conjugate quercetin-3-glucoside, $P < 0.001$). Data are also consistent with the hypothesis that antioxidant activity of free flavonoids is related to the number and position of hydroxyl groups.