

**JOURNAL  
ABSTRACTS****Cellulite****ANATOMY AND PHYSIOLOGY OF SUBCUTANEOUS ADIPOSE TISSUE BY IN VIVO MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY: RELATIONSHIPS WITH SEX AND PRESENCE OF CELLULITE.**

**BACKGROUND:** Little is still known concerning subcutaneous adipose tissue and cellulite, and controversial questions are still under discussion. **AIMS:** Magnetic resonance imaging and spectroscopy were used to address two unresolved questions relating to the anatomy and physiology of subcutaneous adipose tissue. **METHODS:** Using high spatial resolution magnetic resonance imaging we characterized the topography of the dermo- hypodermal junction, and the three-dimensional architecture of the subcutaneous fibrous septae. Using proton spectroscopy, we measured water and lipid fractions within a fat lobule, and T1 and T2 values of the detected compounds. All these data were analysed according to sex and presence of cellulite. **RESULTS:** MR imaging quantified deeper indentations of adipose tissue into the dermis, and evidenced for the first time a great increase in the thickness of the inner fat layer in women with cellulite. Moreover, 3D reconstruction of the fibrous septae network showed a higher percentage of septae in a direction perpendicular to the skin surface in women with cellulite; but our study also depicted the tortuous aspect of this network. MR proton spectroscopy could not show any differences related to sex or presence of cellulite concerning T1 and T2 relaxation times of the detected compounds within a fat lobule, neither the unsaturated lipid fraction, the saturated lipid fraction, nor the water fraction. **CONCLUSIONS:** Magnetic resonance imaging showed that the 3D architecture of fibrous septae couldn't be modelled simply as perpendicular planes for women and tilted planes at 45 degrees for men. MR spectroscopy did not confirm the hypothesis of increased water content in the adipose tissue of women with cellulite as suggested by others, except if such water would be located in the connective septae.

Skin Res Technol. 2002 May;8(2):118-24

**CELLULITE: A REVIEW OF ITS PHYSIOLOGY AND TREATMENT.**

Cellulite affects 85-98% of post-pubertal females of all races. While not a pathologic condition, it remains an issue of cosmetic concern to a great number of individuals. Despite its high prevalence, there have been few scientific investigations into the physiology of cellulite. There have only been a few dozen peer-reviewed articles devoted to cellulite in the medical literature in the past 30 years. There is no definitive explanation for its presentation. This greatly complicates the ability to treat or improve it. The four leading hypotheses that purport to explain the physiology of cellulite include: sexually dimorphic skin architecture, altered connective tissue septae, vascular changes and inflammatory factors. Treatment modalities can be divided into four main categories: attenuation of aggravating factors, physical and mechanical methods, pharmacological agents and laser. There are no truly effective treatments for cellulite.

J Cosmet Laser Ther. 2004 Dec;6(4):181-5

**CELLULITE—THE GREATEST SKIN PROBLEM IN HEALTHY PEOPLE? AN APPROACH.**

Cellulite or so called orange peel skin affects 80-90% of all females. It is not considered as a pathological condition but as aesthetically disturbing dimpling of the skin seen most commonly on the thighs and buttocks. Despite its high prevalence, there have been only a few scientific investigations into the pathophysiology of cellulite reflected in the medical literature. A lack of knowledge regarding specific aetiopathogenetic factors and pathogenesis at large currently limits treatment options. The preferred hypotheses about the origin of cellulite include: gender specific dimorphic skin architecture, altered connective tissue septae, vascular changes and inflammatory processes. The most widely discussed management options include: attenuation of aggravating factors, physical procedures including laser therapy and application of topical incorporating actives. The latter approach has been evidence-based with respect to caffeine liposomal cream and retinol cream.

J Dtsch Dermatol Ges. 2006 Oct;4(10):861-70

**CELLULITE AND SKIN AGEING: IS THERE ANY INTERACTION?**

**Objective:** This study aimed to identify the characteristics of cellulite in women of different age and to appreciate whether cellulite could interfere with skin ageing or not. **Methods:** 94 healthy females, divided into three age groups (21-30yrs; 31-40yrs; 51-60yrs) and two grade groups of cellulite (grade 2; grade 0 or control group), were investigated using non invasive techniques. The "orange peel appearance" was quantified by measuring the shadowed surfaces under low angle light. The biomechanical properties were measured (extensibility-retractability-elasticity). The thicknesses of the skin structures were also evaluated using ultrasound. Echogenicity of the dermis was recorded and dermis density determined in two bands (superficial and low dermis). **Results:** In grade 2, the shadowed surfaces are significantly different according to age; i.e. smaller and more numerous after age of 30; the total skin thickness including hypodermis is increased of about 30% irrespective to age, compared to control group. The biomechanical properties of the skin are significantly modified as age increases without any grade effect. In grade 2, retractability and elasticity parameters are altered from age 30 whilst only from age 50 in the control group. Echogenicities of the superficial and deep dermis also decrease from age 30 and become significantly lower than the ones of grade 0. **Conclusion:** Population with cellulite presents earlier skin ageing characteristics than the control population. Two sub-populations may exist: the under 30 age with large dimpled surfaces, normal biomechanical and density properties; and the over 30 age with smaller and numerous dimpled surfaces and already altered dermis properties. This premature skin ageing should be prevented accordingly.

J Eur Acad Dermatol Venereol. 2008 Feb 25.

### **LICORICE REDUCES SERUM TESTOSTERONE IN HEALTHY WOMEN.**

Licorice has been considered a medicinal plant for thousands of years. The most common side effect is hypokalemic hypertension, which is secondary to a block of 11beta-hydroxysteroid dehydrogenase type 2 at the level of the kidney, leading to an enhanced mineralocorticoid effect of cortisol. We have investigated the effect of licorice on androgen metabolism in nine healthy women 22-26 years old, in the luteal phase of the cycle. They were given 3.5 g of a commercial preparation of licorice (containing 7.6% W.W. of glycyrrhizic acid) daily for two cycles. They were not on any other treatment. Plasma renin activity, serum adrenal and gonadal androgens, aldosterone, and cortisol were measured by radioimmunoassay. Total serum testosterone decreased from 27.8+/-8.2 to 19.0+/-9.4 in the first month and to 17.5+/-6.4 ng/dL in the second month of therapy (p<0.05). It returned to pre-treatment levels after discontinuation. Androstenedione, 17OH-progesterone, and LH levels did not change significantly during treatment. Plasma renin activity and aldosterone were depressed during therapy, while blood pressure and cortisol remained unchanged. **CONCLUSIONS:** Licorice can reduce serum testosterone probably due to the block of 17-hydroxysteroid dehydrogenase and 17-20 lyase. Licorice could be considered an adjuvant therapy of hirsutism and polycystic ovary syndrome.

Steroids. 2004 Oct-Nov;69(11-12):763-6

### **CLINICAL IMPLICATIONS OF GLUCOCORTICOID METABOLISM BY 11BETA-HYDROXYSTEROID DEHYDROGENASES IN TARGET TISSUES.**

11beta-Hydroxysteroid dehydrogenases (11beta-HSD) are microsomal enzymes that catalyze the conversion of active glucocorticoids (GC) to their inactive 11-dehydro products and vice versa. Two isoenzymes of 11beta-HSD have been characterized and cloned in human tissues. The tissue-specific metabolism of GC by these enzymes is important for mineralocorticoid (MC) and GC receptor occupancy and seems to play a crucial role in the pathogenesis of diseases such as apparent MC excess syndrome, and may play roles in hypertension, obesity and impaired hepatic glucose homeostasis. This article reviews the literature and examines the role and importance of 11beta-HSD in humans.

Eur J Endocrinol. 2001 Feb;144(2):87-97

### **A RANDOMIZED, DOUBLE-BLIND,VEHICLE-CONTROLLED, HALF-SIDE COMPARISON WITH A HERBAL OINTMENT CONTAINING MAHONIA AQUIFOLIUM, VIOLA TRICOLOR AND CENTELLA ASIATICA FOR THE TREATMENT OF MILD-TO-MODERATE ATOPIC DERMATITIS.**

**OBJECTIVE:** Only a few clinical trials have been published on the topical treatment of atopic dermatitis with herbal ointments. An ointment containing extracts from Mahonia aquifolium, Viola tricolor and Centella asiatica has previously been studied in open uncontrolled trials with children. However, no data exist on adult patients in a randomized controlled trial. **METHODS:** A total of 88 patients with mild-to-moderate atopic dermatitis were enrolled in a double-blind, vehicle-controlled, randomized, half-side comparison. Patients between 18 and 65 years of age were treated for 4 weeks with an ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica. The primary endpoint was a summary score for erythema, edema/papulation, oozing/crust, excoriation and lichenification according to a 4-point scale. Secondary efficacy variables were assessment of pruritus severity (10 cm VAS) and a global assessment of effectiveness as well as tolerability. **RESULTS:** The study ointment reduced the primary and secondary endpoints slightly more than the base cream which was used as vehicle; the differences were not statistically significant. Since the climatic conditions during the study duration varied from very mild and sunny to very cold and dry, a post-hoc subanalysis was performed with a subset of 64 patients whose treatment was at a mean outside temperature of 10 degrees C or less. Under these conditions the primary endpoint showed high statistical significance. **CONCLUSION:** In this trial, an

ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica could not be proven to be superior to a base cream for patients with mild-to-moderate atopic dermatitis. However, a subanalysis indicated that the cream might be effective under conditions of cold and dry weather.

Int J Clin Pharmacol Ther. 2007 Nov;45(11):583-91

### **EFFECTS OF HORSE-CHESTNUT SEED EXTRACT ON TRANSCAPILLARY FILTRATION IN CHRONIC VENOUS INSUFFICIENCY.**

The effect of horse-chestnut seed extract (standardized on aescin; Venostasin retard) was assessed in a randomized placebo-controlled crossover double-blind trial of 22 patients with proven chronic venous insufficiency by measuring the capillary filtration coefficient and the intravascular volume of the lower leg by venous-occlusion plethysmography. Three hours after taking two capsules of Venostasin (600 mg; each capsule containing 50 mg aescin) the capillary filtration coefficient had decreased by 22%, whereas after administration of an identical-looking placebo capsule it rose but slightly over three hours. The difference in the effect of Venostasin and placebo is statistically significant ( $P = 0.006$ ). The intravascular volume was reduced 5% more after Venostasin than the placebo, but this is not statistically significant. It is concluded that Venostasin has an inhibitory effect on oedema formation via a decrease in transcapillary filtration and thus improves oedema-related symptoms in venous diseases of the legs.

Dtsch Med Wochenschr. 1986 Aug 29;111(35):1321-9

### **COMPARISON OF LEG COMPRESSION STOCKING AND ORAL HORSE-CHESTNUT SEED EXTRACT THERAPY IN PATIENTS WITH CHRONIC VENOUS INSUFFICIENCY.**

**BACKGROUND:** Diseases of the venous system are widespread disorders sometimes associated with modern civilisation and are among the major concerns of social and occupational medicine. This study was carried out to compare the efficacy (oedema reduction) and safety of compression stockings class II and dried horse chestnut seed extract (HCSE, 50 mg aescin, twice daily). **METHODS:** Equivalence of both therapies was examined in a novel hierarchical statistical design in 240 patients with chronic venous insufficiency. Patients were treated over a period of 12 weeks in a randomised, partially blinded, placebo-controlled, parallel study design. **FINDINGS:** Lower leg volume of the more severely affected limb decreased on average by 43.8 mL ( $n = 95$ ) with HCSE and 46.7 mL ( $n = 99$ ) with compression therapy, while it increased by 9.8 mL with placebo ( $n = 46$ ) after 12 weeks therapy for the intention-to-treat group (95% CI: HCSE: 21.1-66.4; compression: 30.4-63.0; placebo: 40.0-20.4). Significant oedema reductions were achieved by HCSE ( $p = 0.005$ ) and compression ( $p = 0.002$ ) compared to placebo, and the two therapies were shown to be equivalent ( $p = 0.001$ ); in this design, however, compression could not be proven as standard with regard to oedema reduction in the statistical test procedure. Both HCSE and compression therapy were well tolerated and no serious treatment-related events were reported. **INTERPRETATION:** These results indicate that compression stocking therapy and HCSE therapy are alternative therapies for the effective treatment of patients with oedema resulting from chronic venous insufficiency.

Lancet. 1996 Feb 3;347(8997):292-4

### **ANTIOXIDATIVE AND ANTIGENOTOXIC EFFECTS OF JAPANESE HORSE CHESTNUT (AESCULUS TURBINATA) SEEDS.**

Japanese horse chestnut seed extract (HCSE) dose-dependently inhibited the autooxidation of linoleic acid (IC<sub>50</sub>): 0.2 mg/ml), and the inhibition was almost complete at a concentration of 1 mg/ml. The HCSE scavenged DPPH (1,1-diphenyl-2-picrylhydrazyl) radicals and superoxide anions with EC<sub>50</sub>s of 0.65 and 0.21 mg/ml, respectively. However, it had no effect on hydrogen peroxide. The HCSE inhibited the genotoxicities of furylfuramide, N-methyl-N-nitrosourea, methyl methanesulfonate, mitomycin C, 2-aminoanthracene and aflatoxin B1 at a concentration of 1 mg/ml or more. Total polyphenol content of the HCSE was 21 mg/g (13 mg/g-seeds). These results indicate that the Japanese horse chestnut seed is an antioxidative and antimutagenic botanical resource.

J Vet Med Sci. 2005 Jul;67(7):731-4

**VITAMIN D RECEPTOR GENE POLYMORPHISMS AND HAPLOTYPES AND POSTMENOPAUSAL BREAST CANCER RISK.**

**INTRODUCTION:** Vitamin D receptor (VDR) genotypes may influence breast cancer risk by altering potential anticarcinogenic effects of vitamin D, but epidemiological studies have been inconsistent. Effect modification by serum 25-hydroxyvitamin D (25 [OH]D), the biomarker for vitamin D status in humans, has rarely been examined. **METHODS:** We assessed the effects of two frequently analyzed polymorphisms (FokI and TaqI) and two potentially functional variants (VDR-5132 and Cdx2) in the VDR gene, which thus far have not been analyzed with respect to breast cancer risk, on postmenopausal breast cancer risk in a population-based, case-control study including 1,408 patients (cases) and 2,612 control individuals (controls) matched for year of birth. Odds ratios (ORs) for breast cancer adjusted for potential confounders were calculated for genotypes and estimated haplotypes. **RESULTS:** No differences in serum 25(OH)D concentrations by VDR genotype were observed. None of the analyzed polymorphisms was associated with overall risk for postmenopausal breast cancer. However, the TaqI polymorphism was associated with a significantly increased risk for oestrogen receptor positive tumours (OR = 1.18, 95% confidence interval [CI] = 1.00 to 1.38, comparing t allele carriers with noncarriers) but not for oestrogen receptor negative tumours (OR = 0.88, 95% CI = 0.69 to 1.13; P for interaction = 0.04). Haplotype analysis revealed the haplotype FtCA (FokI F, TaqI t, VDR-5132 C, Cdx2 A), which contains the TaqI t allele, to be associated with a significantly greater breast cancer risk as compared with the most frequent haplotype FTCC (OR = 1.43, 95% CI = 1.00 to 2.05). No significant interaction between VDR genotypes or haplotypes and 25(OH)D was observed. **CONCLUSION:** Our results support potential effects of VDR polymorphisms on postmenopausal breast cancer risk and possible differential effects of receptor status of the tumour. However, further studies focusing on the influence of polymorphisms and haplotypes on VDR functionality, activity and concentration are needed.

Breast Cancer Res. 2008;10(2):R31

**VITAMIN D AND CALCIUM SUPPLEMENTATION REDUCES CANCER RISK: RESULTS OF A RANDOMIZED TRIAL.**

**BACKGROUND:** Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking. **OBJECTIVE:** The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types. **DESIGN:** This was a 4-y, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1,179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged >55 y in a 9-county rural area of Nebraska centered at latitude 41.4 degrees N. Subjects were randomly assigned to receive 1,400-1,500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 1,100 IU vitamin D3/d (Ca + D), or placebo. **RESULTS:** When analyzed by intention to treat, cancer incidence was lower in the Ca + D women than in the placebo control subjects (P < 0.03). With the use of logistic regression, the unadjusted relative risks (RR) of incident cancer in the Ca + D and Ca-only groups were 0.402 (P = 0.01) and 0.532 (P = 0.06), respectively. When analysis was confined to cancers diagnosed after the first 12 mo, RR for the Ca + D group fell to 0.232 (CI: 0.09, 0.60; P < 0.005) but did not change significantly for the Ca-only group. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk. **CONCLUSIONS:** Improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as NCT00352170.

Am J Clin Nutr. 2007 Jun;85(6):1586-91

**GLYCEMIC LOAD, GLYCEMIC INDEX, AND THE RISK OF BREAST CANCER AMONG MEXICAN WOMEN.**

**OBJECTIVE:** The amount and composition of dietary carbohydrates is a major determinant of postprandial blood glucose and insulin, and risk of breast cancer has been positively associated with plasma levels of insulin and insulin-like growth factor 1. We sought to evaluate dietary glycemic load (GL) and overall glycemic index (GI) in relation to breast cancer risk in Mexican women. **METHODS:** We examined dietary GL and overall GI and breast cancer risk among 475 women with histologically-confirmed breast cancer and a random sample of 1,391 women from Mexico City households. Diet was assessed using a food frequency questionnaire adapted to the Mexican population. **RESULTS:** The multivariate adjusted or for all women comparing the highest quartile of dietary GL with the lowest quartile was 1.62 (95% CI 1.13-2.32; p-test for trend = 0.02) with a significant trend. In postmenopausal women, the multivariate adjusted or comparing the extreme quartiles was 2.18 (95% CI 1.34-3.55; p-test for

trend=0.005). Overall GI was not significantly associated with risk of breast cancer. CONCLUSION: High intake of rapidly absorbed carbohydrate appears to play an important role in the risk of breast cancer in Mexican women.

Cancer Causes Control. 2005 Dec;16(10):1165-9

### **CONSUMPTION OF DAIRY PRODUCTS AND THE RISK OF BREAST CANCER: A REVIEW OF THE LITERATURE.**

Differences in eating patterns and breast cancer rates across countries suggest that several dietary components, including dairy products, could affect breast cancer risk. However, dairy products are a diverse food group in terms of the factors that could potentially influence risk. Some dairy products, such as whole milk and many types of cheese, have a relatively high saturated fat content, which may increase risk. Moreover, milk products may contain contaminants such as pesticides, which have carcinogenic potential, and growth factors such as insulin-like growth factor I, which have been shown to promote breast cancer cell growth. In contrast, the calcium and vitamin D contents of dairy products have been hypothesized to reduce breast cancer risk. We reviewed the current epidemiologic literature on the relation between dairy product intakes and breast cancer risk, focusing primarily on the results of cohort and case-control studies. Most of the studies reviewed showed no consistent pattern of increased or decreased breast cancer risk with a high consumption of dairy products as a whole or when broken down into high-fat and low-fat dairy products, milk, cheese, or butter. Measurement error may have attenuated any modest association with dairy products. The available epidemiologic evidence does not support a strong association between the consumption of milk or other dairy products and breast cancer risk.

Am J Clin Nutr. 2004 Jul;80(1):5-14

### **CONSUMPTION OF SWEET FOODS AND BREAST CANCER RISK IN ITALY.**

**BACKGROUND:** The relation between the intake of sugar and sweets and the risk of breast cancer has been considered in ecological, prospective and case-control studies, but the results are unclear. We analyzed such a relation in a case-control study conducted between 1991 and 1994 in Italy. **PATIENTS AND METHODS:** Cases were 2,569 women with histologically confirmed incident breast cancer and controls were 2,588 women admitted to hospital for acute, non-neoplastic, non-hormone-related conditions. Information on diet was based on an interviewer-administered questionnaire tested for reproducibility and validity. The odds ratios (OR) and 95% confidence intervals (CI) were computed by multiple logistic regression equations. **RESULTS:** Compared with women with the lowest tertile of intake, women in the highest tertile of intake of desserts (including biscuits, brioches, cakes, puffs and ice-cream) and sugars (including sugar, honey, jam, marmalade and chocolate) had multivariate ORs of 1.19 (95% CI 1.02-1.39) and 1.19 (95% CI 1.02-1.38), respectively. The results were similar in strata of age, body mass index, total energy intake and other covariates. **CONCLUSIONS:** We found a direct association between breast cancer risk and consumption of sweet foods with high glycemic index and load, which increase insulin and insulin growth factors.

Ann Oncol. 2006 Feb;17(2):341-5

### **SERUM ENTEROLACTONE LEVELS AND THE RISK OF BREAST CANCER IN WOMEN WITH PALPABLE CYSTS.**

Low levels of lignans, namely enterolactone, have been reported to be associated with an increased risk of breast cancer in the general female population. We assessed, retrospectively, the relationship between serum enterolactone concentrations and the occurrence of breast cancer in women with palpable cysts. The levels of enterolactone in cryopreserved serum aliquots, obtained from 383 women with palpable cysts at the time of their first cyst aspiration, were measured using a time-resolved fluoroimmunoassay (TR-FIA). After a median follow-up time of 6.5 years (range 0.5-12.75 years), 18 women were found to have developed an invasive breast cancer. Median values of serum enterolactone were significantly lower in women who subsequently developed breast cancer: 8.5 nM/l versus 16.0 nM/l:  $P=0.04$ . Odd Ratios (OR) for breast cancer were: 0.36 ( $P=0.03$ ), 0.57 ( $P=0.3$ ) and 0.38 ( $P=0.25$ ) for 25th (8 nM/l), 50th (16 nM/l) and 75th (24 nM/l) percentile values, respectively. The receiver operating characteristic (ROC) analysis showed a satisfactory accuracy for enterolactone as a breast cancer risk indicator (area under the curve (AUC)=0.64:  $P=0.04$ ). Logistic regression analysis confirmed that the enterolactone concentration had a strong protective effect on the breast cancer risk. These findings may have important clinical implications with regard to interventional diet-focused chemo-preventive trials.

Eur J Cancer. 2004 Jan;40(1):84-9

### **DIETARY LIGNAN INTAKES AND RISK OF PRE- AND POSTMENOPAUSAL BREAST CANCER.**

Lignans are plant compounds metabolized in the mammalian gut to produce the phytoestrogens enterolactone and enterodiol. Because estrogens have been linked to breast cancer etiology, lignans could affect breast cancer risk through modulation of endogenous estrogen metabolism or competitive inhibition with estrogen receptors. We examined breast cancer risk and dietary lignan intake in a population-based case-control study of 1,122 women with primary, incident, histologically confirmed breast cancer and 2,036 controls frequency matched to cases on age and county of residence as part of the Western New York

Exposures and Breast Cancer (WEB) Study. Diet was assessed with a self-administered 104-item food frequency questionnaire and other relevant data were collected by detailed in-person interviews. Lignans were expressed as the sum of the dietary precursors secoisolariciresinol and matairesinol. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by unconditional logistic regression, adjusting for age, total energy and other breast cancer risk factors. Premenopausal women in the highest quartile of dietary lignan intake had reduced breast cancer risk (OR = 0.66; 95% CI = 0.44-0.98). No association was observed between lignan intakes and postmenopausal breast cancer. Our results suggest that dietary lignans may be important in the etiology of breast cancer, particularly among premenopausal women.

Int J Cancer. 2004 Sep 1;111(3):440-3

### **PILOT STUDY: EFFECT OF 3,3'-DIINDOLYLMETHANE SUPPLEMENTS ON URINARY HORMONE METABOLITES IN POSTMENOPAUSAL WOMEN WITH A HISTORY OF EARLY-STAGE BREAST CANCER.**

Dietary indoles, present in Brassica plants such as cabbage, broccoli, and Brussels sprouts, have been shown to provide potential protection against hormone-dependent cancers. 3,3'-Diindolylmethane (DIM) is under study as one of the main protective indole metabolites. Postmenopausal women aged 50-70 yr from Marin County, California, with a history of early-stage breast cancer, were screened for interest and eligibility in this pilot study on the effect of absorbable DIM (BioResponse-DIM) supplements on urinary hormone metabolites. The treatment group received daily DIM (108 mg DIM/day) supplements for 30 days, and the control group received a placebo capsule daily for 30 days. Urinary metabolite analysis included 2-hydroxyestrone (2-OHE1), 16-alpha hydroxyestrone (16alpha-OHE1), DIM, estrone (E1), estradiol(E2), estriol (E3), 6beta-hydroxycortisol (6beta-OHC), and cortisol in the first morning urine sample before intervention and 31 days after intervention. Nineteen women completed the study, for a total of 10 in the treatment group and 9 in the placebo group. DIM-treated subjects, relative to placebo, showed a significant increase in levels of 2-OHE1 (P=0.020), DIM (P=0.045), and cortisol (P=0.039), and a nonsignificant increase of 47% in the 2-OHE1/16alpha-OHE1 ratio from 1.46 to 2.14 (P=0.059). In this pilot study, DIM increased the 2-hydroxylation of estrogen urinary metabolites.

Nutr Cancer. 2004;50(2):161-7

### **A PHASE I STUDY OF INDOLE-3-CARBINOL IN WOMEN: TOLERABILITY AND EFFECTS.**

We completed a phase I trial of indole-3-carbinol (I3C) in 17 women (1 postmenopausal and 16 premenopausal) from a high-risk breast cancer cohort. After a 4-week placebo run-in period, subjects ingested 400 mg I3C daily for 4 weeks followed by a 4-week period of 800 mg I3C daily. These chronic doses were tolerated well by all subjects. Hormonal variables were measured near the end of the placebo and dosing periods, including determination of the urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio. Measurements were made during the follicular phase for premenopausal women. Serum estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, and sex hormone binding globulin showed no significant changes in response to I3C. Caffeine was used to probe for cytochrome P450 1A2 (CYP1A2), N-acetyltransferase-2 (NAT-2), and xanthine oxidase. Comparing the results from the placebo and the 800 mg daily dose period, CYP1A2 was elevated by I3C in 94% of the subjects, with a mean increase of 4.1-fold. In subjects with high NAT-2 activities, these were decreased to 11% by I3C administration but not altered if NAT-2 activity was initially low. Xanthine oxidase was not affected. Lymphocyte glutathione S-transferase activity was increased by 69% in response to I3C. The apparent induction of CYP1A2 was mirrored by a 66% increase in the urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio in response to I3C. The maximal increase was observed with the 400 mg daily dose of I3C, with no further increase found at 800 mg daily. If the ratio of hydroxylated estrone metabolites is a biomarker for chemoprevention, as suggested, then 400 mg I3C daily will elicit a maximal protective effect.

Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1953-60

### **PLASMA 25-HYDROXYVITAMIN D AND 1,25-DIHYDROXYVITAMIN D AND RISK OF BREAST CANCER.**

Several lines of evidence suggest that vitamin D may reduce incidence of breast cancer, but few epidemiologic studies have addressed the relation of plasma vitamin D metabolites to the risk of this disease. We prospectively examined the relationship between plasma levels of 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25(OH)2D] and risk of breast cancer in a case-control study nested within the Nurses' Health Study cohort. Blood samples were collected from study participants in 1989-1990. Breast cancer cases developing between blood collection and June 1, 1996, were matched to cancer-free controls on the basis of age, menopausal status, and other factors. Stored plasma samples from 701 cases and 724 controls were available for metabolite analysis. Cases had a lower mean 25(OH)D level than controls (P=0.01), but mean 1,25(OH)2D levels were similar (P=0.49). High levels of both metabolites were associated with a nonsignificant lower risk of breast cancer. Women in the highest quintile of 25(OH)D had a relative risk of 0.73 (95% confidence interval=0.49-1.07; P<sub>trend</sub>=0.06) compared with those in the lowest quintile. For 1,25(OH)2D, the comparable relative risk was 0.76 (95% confidence interval=0.52-1.11; P<sub>trend</sub>=0.39). For both metabolites, the association was stronger in women ages 60 years and older, but results were not statistically significant. Our findings suggest that high levels of 25(OH)D, and perhaps 1,25(OH)2D, may be modestly associated with reduced risk of breast cancer.

### **25(OH)D3 AND 1,25(OH)2D3 SERUM CONCENTRATION AND BREAST TISSUE EXPRESSION OF 1ALPHA-HYDROXYLASE, 24-HYDROXYLASE AND VITAMIN D RECEPTOR IN WOMEN WITH AND WITHOUT BREAST CANCER.**

1,25(OH)2D3 is an antiproliferative agent that may inhibit proliferation of breast cancer (BC) cells in vitro and BC development in animals. Epidemiological studies have shown a high incidence of BC in people less exposed to solar rays. To unravel the role of Vitamin D3 in BC patients, we have investigated serum levels of 25(OH)D3 and its active form 1,25(OH)2D3 as well as tissue expression of 1alpha-hydroxylase, 24-hydroxylase, and Vitamin D-receptor (VDR), determined by semiquantitative RT-PCR, in 88 Brazilian BC patients and 35 women without cancer (submitted to mammoplasties or resection of benign lesions). Median age of women with and without cancer was 51 and 46 years, respectively, and the majority of BC patients were classified as clinical stage II (67%). Although no differences in 25(OH)D3 serum concentration were found, 1,25(OH)2D3 (40+/-21 pg/ml) levels in BC patients were lower than in women without cancer (53+/-23). Our results indicate that 24-hydroxylase, VDR and 1alpha-hydroxylase mRNA tissue expression is similar in both groups and no correlation between 24-hydroxylase, 1alpha-hydroxylase, and VDR expression in breast tumors was found. A low 1,25(OH)2D3 serum concentration seems to be associated to breast cancer, however, the mechanism involved in this regulation is still unclear.

J Steroid Biochem Mol Biol. 2006 Aug;100(4-5):184-92

### **PREVENTION AND ANTI-AGING IN ENDOCRINOLOGY.**

The aging process is associated with a characteristic decline in the levels of certain hormones. In both sexes, growth hormones, melatonin, dehydroepiandrosterone (DHEA) and its sulfate compound DHEAS reach their maximum levels in the third decade of life, and then decline progressively. In addition, a constant decrease in the production of biologically active free testosterone of approximately 1% per year is observed in men. The abrupt cessation of sex hormone production seen in women is not observed in men. Irrespective of the hormone being supplemented, it should always be remembered that not merely the hormone-producing organ, but also the target tissue has aged, and may thus manifest a different reaction to the substituted hormone than youthful tissue.

MMW Fortschr Med. 2007 Mar 1;149(9):33-5

### **SYMPTOMS ASSOCIATED WITH MENOPAUSAL TRANSITION AND REPRODUCTIVE HORMONES IN MIDLIFE WOMEN.**

**OBJECTIVE:** To test the hypothesis that prevalence of women with menopausal symptoms of hot flushes; aches, joint pain, and stiffness; depressed mood; poor sleep; decreased libido; or vaginal dryness increases with progression through the menopausal transition. **METHODS:** Women in the Penn Ovarian Aging Study were assessed longitudinally for 9 years. Data were obtained from structured interviews, a validated symptom questionnaire, menstrual bleeding dates and early follicular hormone measures (estradiol [E2], follicle-stimulating hormone [FSH], and inhibin b). Menopausal stages were based on menstrual bleeding patterns. Other risk factors included age, race, history of depression, current smoking, body mass index, and perceived stress. Generalized linear regression models for repeated measures were used to estimate associations among the variables with each symptom. **RESULTS:** The prevalence of hot flushes; aches, joint pain, and stiffness; and depressed mood increased in the menopausal transition. Menopausal stage was associated with hot flushes ( $P < .001$ ); aches joint pain, and stiffness ( $P < .001$ ); and depressed mood ( $P = .002$ ). Within-woman fluctuations of E2 were associated with hot flushes and aches. Poor sleep, decreased libido, and vaginal dryness were not associated with menopausal stages. There was 80% power to detect an absolute difference of 11% for libido and vaginal dryness and 17% for poor sleep in the prevalence of these symptoms in the late menopausal transition compared with premenopausal status. **CONCLUSION:** The study highlights the role of menopausal stages for some symptoms of midlife women and indicates that stages in the transition to menopause are associated with hot flushes; aches, joint pain, and stiffness; and depressed mood. Fluctuations of E2, decreased levels of inhibin b, and increased FSH levels were associated with these symptoms. **LEVEL OF EVIDENCE:** II.

Obstet Gynecol. 2007 Aug;110(2 Pt 1):230-40

### **THE EFFECTS OF ORAL AND TRANSDERMAL HORMONE REPLACEMENT THERAPY ON C-REACTIVE PROTEIN LEVELS AND OTHER INFLAMMATORY MARKERS IN WOMEN WITH HIGH RISK OF THROMBOSIS.**

**INTRODUCTION:** In the estrogen in venous thromboembolism (EVTET) study of 140 women with a history of venous thromboembolism (VTE), oral hormone replacement therapy (HRT) was associated with strong activation of coagulation markers and increased risk of recurrent VTE. No such associations were observed in the estrogen women atherosclerosis (EWA) study of 118 women with established coronary artery disease who were given transdermal HRT. **OBJECTIVES AND METHODS:** The aim

of the present study was to evaluate the effects of oral and transdermal HRT on levels of C-reactive protein (CRP), which was assayed with a highly sensitive method. We also evaluated the effects on other inflammatory markers and the influence of possible confounding factors. RESULTS: Oral HRT was associated with a significant increase in CRP after 3 months as compared with placebo (median 79% [95% confidence interval 36-119%] versus -4% [-13 to 10%],  $p = 0.001$ ). These changes sustained after 12 months. Among those allocated HRT, the median increase in CRP was higher in women who subsequently developed recurrent thrombosis (median 328%,  $n = 5$ , versus 54%,  $n = 60$ ). TNF-alpha levels decreased significantly by mean -10% [-15 to -5%] versus 3% [-4 to 10%],  $p=0.004$ . Soluble VCAM-1 decreased in the HRT group compared to the placebo group (mean -13% [-18 to -8%] versus 1%, [-3 to 5%],  $p < 0.001$ ). There were no significant changes in levels of IL-6, TGF-beta or P-selectin. On transdermal HRT no significant changes in CRP were observed after 3 and 12 months of treatment. CONCLUSIONS: Our findings substantiate that oral HRT containing estradiol is associated with a marked and rapid increase in CRP, whereas transdermal treatment is not. However, this increase on oral treatment was associated with no increases of other inflammatory markers.

Maturitas. 2005 Oct 16;52(2):111-8

### **DIFFERENTIAL EFFECTS OF ORAL VERSUS TRANSDERMAL ESTROGEN REPLACEMENT THERAPY ON C-REACTIVE PROTEIN IN POSTMENOPAUSAL WOMEN.**

OBJECTIVES: We investigated whether the route of estrogen replacement therapy (ET) is the major determinant of C-reactive protein (CRP) in postmenopausal women. BACKGROUND: Recent studies demonstrated that oral ET causes a sustained increase in CRP, implicating a proinflammatory effect. Because CRP is synthesized in the liver, we hypothesized that estrogen-induced CRP elevation is related to first-pass hepatic metabolism. METHODS: In 21 postmenopausal women, we conducted a randomized, crossover, placebo-controlled study to compare the effects of transdermal versus oral ET on CRP and inflammatory cytokines. We measured CRP, interleukin (IL)-1-beta, IL-6, and tumor necrosis factor-alpha before and after eight weeks of transdermal estradiol (E(2)) (100 microg/day), oral conjugated estrogen (CEE) (0.625 mg/day), or placebo. Insulin-like growth factor-1 (IGF-1), a hepatic-derived anabolic peptide, was also measured. RESULTS: Transdermal E(2) had no effect on CRP or IGF-1 levels. In contrast, eight weeks of oral conjugated estrogens caused a more than twofold increase in CRP and a significant reduction in IGF-1 ( $p < 0.01$ ) in the same women. The magnitude of increase in CRP was inversely correlated to the decrease in IGF-1 ( $r = -0.49$ ,  $p = 0.008$ ). Neither transdermal E(2) nor oral CEE had any effects on the plasma concentrations of cytokines that promote CRP synthesis. CONCLUSIONS: In postmenopausal women, oral but not transdermal ET increased CRP by a first-pass hepatic effect. An increase in CRP levels is accompanied by a reduction in IGF-1, an anti-inflammatory growth factor. Because CRP is a powerful predictor of an adverse prognosis in otherwise healthy postmenopausal women, the route of administration may be an important consideration in minimizing the adverse effects of ET on cardiovascular outcomes.

J Am Coll Cardiol. 2003 Apr 16;41(8):1358-63

**Melatonin****MELATONIN PREVENTS LEARNING DISORDERS IN BRAIN-LESIONED NEWBORN MICE.**

Perinatal brain injuries often result in irreversible learning disabilities, which manifest in early childhood. These injuries are chiefly ascribable to marked susceptibility of the immature brain to glutamate-induced excitotoxicity. No treatments are available. One well-characterized model of perinatal brain injuries consists in injecting the glutamate analog ibotenate into the brain of 5-day-old mice. The resulting excitotoxic lesions resemble the hypoxic-ischemic gray-matter lesions seen in full-term and near-term newborns, as well as the white-matter lesions of preterm newborns. We previously reported that these lesions disrupted odor preference conditioning in newborn mice. The aim of this study was to assess the effectiveness of the neuroprotector melatonin in preventing learning disabilities in newborn mice with ibotenate-induced brain injury. In postnatal day (P) 6-P7 pups, we tested psychomotor reflexes, spontaneous preference for maternal odors as an index of memory, ultrasonic vocalization responses to stroking as an index of sensitivity to tactile stimuli, and conditioned preference for an odor previously paired with stroking as an index of learning abilities. Without melatonin, conditioning was abolished, whereas spontaneous odor preference, psychomotor reflexes, and sensitivity to tactile stimuli were normal. Thus, abolition of conditioning was not associated with sensorimotor impairments. Histological analysis confirmed the efficacy of melatonin in reducing white-matter lesions induced by ibotenate. Furthermore, treatment with melatonin protected the ability to develop conditioning. Thus, melatonin, which easily crosses the blood-brain barrier and has been proven safe in children, may be effective in preventing learning disabilities caused by perinatal brain injuries in human preterm infants.

Neuroscience. 2007 Dec 12;150(3):712-9

**PROTECTIVE EFFECT OF MELATONIN AGAINST HEAD TRAUMA-INDUCED HIPPOCAMPAL DAMAGE AND SPATIAL MEMORY DEFICITS IN IMMATURE RATS.**

It is well known that head trauma induces the cognitive dysfunction resulted from hippocampal damage. In the present study, we aimed to demonstrate the effect of melatonin on hippocampal damage and spatial memory deficits in 7-day-old rat pups subjected to contusion injury. Melatonin was injected intraperitoneally at the doses of 5 or 20 mg/kg of body weight immediately after induction of traumatic injury. Hippocampal damage was examined by cresyl violet staining and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay. Spatial memory performance was assessed in the Morris water maze. Melatonin significantly attenuated trauma-induced neuronal death in hippocampal CA1, CA3 regions and dentate gyrus, and improved spatial memory deficits, which was equally effective at doses of 5-20 mg/kg. The present results suggest that melatonin is a highly promising agent for preventing the unfavorable outcomes of traumatic brain injury in young children.

Neurosci Lett. 2005 Sep 16;385(3):234-9

**DOES MELATONIN PROTECT OR TREAT BRAIN DAMAGE FROM TRAUMATIC OXIDATIVE STRESS?**

A variety of experimental studies have demonstrated the neuroprotective effects of melatonin, based on its antioxidant activity. In a prospective randomized study, the effects of melatonin were investigated in experimental head trauma-induced oxidative stress in rabbits. The experimental study was performed on 30 rabbits. The animals were divided into three groups. Group I (sham procedure): a right parietal craniotomy was performed on each animal, and the dura mater was left intact. Group II: experimental brain trauma (EBT) was performed on each animal using a 1 cm inner diameter x 10 cm long glass tube, through which a 20 g weight (0.5 cm diameter) was dropped onto the brain at the craniotomy site, causing a contusional head trauma. Group III: the same EBT model was performed, but 2.5 mg/kg melatonin was injected intraperitoneally four times (total dose 10 mg/kg); these injections were performed 20 min before the operation, during the trauma, 1 h later and 2 h later. The rabbits were sacrificed after the EBT at 24 h after the brain trauma. The activities of the three principal antioxidant enzymes-catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px)-were determined, and the levels of malondialdehyde (MDA), a product of lipid peroxidation, and glutathione (GSH) were measured in brain homogenates. MDA levels were found to be higher in the EBT group than in the EBT+melatonin group or the sham procedure group. The SOD activity was found to be higher in the EBT group than in the sham procedure group. Enzymatic parameters (except for SOD) were significantly higher in melatonin-treated animals than in EBT animals. GSH levels in melatonin-treated animals were decreased compared with EBT animals. In conclusion, the data indicate that melatonin protects against free radical-mediated oxidative changes in brain tissue by boosting antioxidant enzymes, and in particular lowering lipid peroxidation in rabbits with EBT.

### **MELATONIN SECRETION AFTER HEAD INJURY: A PILOT STUDY.**

**PRIMARY OBJECTIVE:** To investigate the circadian rhythm of serum melatonin in patients with traumatic brain injury (TBI) during Intensive Care Unit (ICU) stay and its relationship with core body temperature fluctuations and measures of severity of their condition. **METHODS AND PROCEDURES:** The pilot study was conducted in the ICU of a general hospital in Athens, Greece. Blood melatonin was determined in eight patients consecutively admitted at the ICU following severe head injury, eight times per day during the first and second day following admission. Core body temperature was recorded at hourly intervals. Patients were also assessed with the Glasgow Coma Score (GCS) and the APACHE II score. **RESULTS:** Melatonin concentrations were lower than the normally reported values. Mean night-time melatonin levels were higher than mean daytime levels both on the first and second days, although not statistically significant. Diurnal variation of melatonin was associated with the GCS. Thus, patients with low GCS ( $n = 4$ ) did not exhibit a consistent diurnal variation of melatonin, whereas those with high GCS ( $n = 4$ ) retained the normally expected fluctuations. **CONCLUSIONS:** ICU-treated TBI patients exhibit reduced melatonin levels and a circadian secretion profile which is related to the severity of the injury. Patients with more severe head trauma exhibit a clearly disrupted pattern of melatonin secretion, whereas those with less severe trauma preserve a relatively intact diurnal rhythm. Furthermore, the diurnal secretion pattern of melatonin appeared to be dissociated from the circadian rhythm of core body temperature. These preliminary findings may have implications for the management of TBI patients.

Brain Inj. 2006 Jul;20(8):873-8

### **MELATONIN PROTECTS AGAINST ISCHEMIA/REPERFUSION-INDUCED OXIDATIVE DAMAGE TO MITOCHONDRIA IN FETAL RAT BRAIN.**

We investigated the effects of melatonin on ischemia/reperfusion-induced oxidative damage to mitochondria in fetal rat brain. The utero-ovarian arteries were occluded bilaterally for 20 min in female Wistar rats on day 19 of pregnancy to induce fetal ischemia. Reperfusion was achieved by releasing the occlusion and restoring circulation for 30 min. A sham operation was performed in control rats. Melatonin (10 mg/kg) or vehicle was injected intraperitoneally 60 min prior to occlusion. We measured the respiratory control index (RCI) and the adenosine 5-diphosphate (ADP)/oxygen ratio as indicators of mitochondrial respiratory activity, as well as the concentration of thiobarbituric acid-reactive substances (TBARS) in the mitochondria of fetal brain. Ischemia/reperfusion significantly elevated the concentration of TBARS and significantly reduced the RCI as well as the ADP/oxygen ratio. Melatonin treatment reversed the ischemia/reperfusion-induced reductions in the RCI ( $2.29 \pm 0.06$ - $2.64 \pm 0.09$ ,  $P < 0.05$ ) and in the ADP/oxygen ratio ( $1.48 \pm 0.03$ - $1.57 \pm 0.02$ ,  $P < 0.05$ ), and also reduced the elevation in concentration of TBARS ( $11.00 \pm 0.34$ - $7.57 \pm 0.74$  nM/mg protein,  $P < 0.01$ ), resulting in values similar to those in untreated, sham-ischemic animals. The results indicate that administration of melatonin to pregnant rats may prevent ischemia/reperfusion-induced oxidative mitochondrial damage in fetal rat brain.

J Pineal Res. 2001 Sep;31(2):167-72

### **EFFECT OF MELATONIN ON BRAIN OXIDATIVE DAMAGE INDUCED BY TRAUMATIC BRAIN INJURY IN IMMATURE RATS.**

Progressive compromise of antioxidant defenses and free radical-mediated lipid peroxidation, which is one of the major mechanisms of secondary traumatic brain injury (TBI), has also been reported in pediatric head trauma. In the present study, we aimed to demonstrate the effect of melatonin, which is a potent free radical scavenger, on brain oxidative damage in 7-day-old rat pups subjected to contusion injury. Whereas TBI significantly increased thiobarbituric acid reactive substances (TBARS) levels, there was no compensatory increase in the antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) 24 hours after TBI in 7-day-old rats. Melatonin administered as a single dose of 5 mg/kg prevented the increase in TBARS levels in both non-traumatized and traumatized brain hemispheres. In conclusion, melatonin protects against oxidative damage induced by TBI in the immature brain.

Physiol Res. 2005;54(6):631-7

### **MELATONIN ACCELERATES THE PROCESS OF WOUND REPAIR IN FULL-THICKNESS INCISIONAL WOUNDS.**

The pineal gland hormone melatonin is known to have both anti-inflammatory and immunomodulatory effects. Given this, we propose that melatonin is an ideal candidate to enhance the process of wound healing. The present study assessed the effects of exogenously administered melatonin (1.2 mg/kg intra-dermal), on scar formation using a full-thickness incisional rat model of dermal wound healing. Melatonin treatment significantly improved the quality of scarring, both in terms of maturity and orientation of collagen fibres. An increase in nitric oxide synthase (NOS) activity and therefore nitric oxide production is detrimental during inflammation but is favourable during granulation tissue formation. Melatonin treatment significantly decreased inducible NOS (iNOS) activity during the acute inflammatory phase but significantly increased iNOS activity during the resolving phase.

Cyclooxygenase-2, which has been shown to have anti-inflammatory effects, was elevated in the melatonin-treated rats following wounding. In addition, melatonin treatment also accelerated the angiogenic process, increasing the formation of new blood vessels and elevating the level of vascular endothelial growth factor protein expression during granulation tissue formation. Melatonin treatment increased arginase activity (which generates proline, a building block for collagen synthesis) from earlier time points. The protein profiles of hemoxygenase-1 (HO-1) and HO-2 isoforms, vital participants in the repair process, were also up-regulated upon melatonin treatment. This study has therefore demonstrated, for the first time, that melatonin can significantly improve the quality of wound healing and scar formation.

J Pineal Res. 2008 May;44(4):387-96

### **ANTI-INFLAMMATORY ACTIONS OF MELATONIN AND ITS METABOLITES, N1-ACETYL-N2-FORMYL-5-METHOXYKYNURAMINE (AFMK) AND N1-ACETYL-5-METHOXYKYNURAMINE (AMK), IN MACROPHAGES.**

Inflammation is a complex phenomenon involving multiple cellular and molecular interactions which must be tightly regulated. Cyclooxygenase-2 (COX) is the key enzyme that catalyzes the two sequential steps in the biosynthesis of PGs from arachidonic acid. The inducible isoform of COX, namely COX-2, plays a critical role in the inflammatory response and its over-expression has been associated with several pathologies including neurodegenerative diseases and cancer. Melatonin is the main product of the pineal gland with well documented antioxidant and immuno-modulatory effects. Since the action of the indole on COX-2 has not been previously described, the goal of the present report was to test the effect of melatonin on the activities of COX-2 and inducible nitric oxide synthase (iNOS), using lipopolysaccharide (LPS)-activated RAW 264.7 macrophages as a model. Melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), prevented COX-2 activation induced by LPS, without affecting COX-1 protein levels. The structurally related compound 6-methoxy-melatonin only partially prevented the increase in COX-2 protein levels induced by the toxin. Likewise melatonin prevented iNOS activation and reduced the concentration of products from both enzymes, PGE(2) and nitric oxide. Another endogenous antioxidant like N-acetyl-cysteine (NAC) did not reduced COX-2 significantly. The current finding corroborates a role of melatonin as an anti-inflammatory agent and, for the first time, COX-2 and iNOS as molecular targets for either melatonin or its metabolites AFMK and AMK. These anti-inflammatory actions seem not to be exclusively mediated by the free radical scavenging properties of melatonin. As a consequence, the present work suggests these substances as a new class of potential anti-inflammatory agents without the classical side effects due to COX-1 inhibition.

J Neuroimmunol. 2005 Aug;165(1-2):139-49

### **MELATONIN: POTENTIAL FUNCTIONS IN THE ORAL CAVITY.**

**BACKGROUND:** Melatonin is synthesized and secreted by the pineal gland and other organs. The pattern of melatonin secretion is controlled by an endogenous circadian timing system and conveys information about the light-dark cycle to the organism, thereby organizing its seasonal and circadian rhythms. Melatonin has powerful antioxidant effects, functions in an immunomodulatory role, may protect against certain cancers, delays some age-related processes, stimulates the synthesis of type I collagen fibers, and promotes bone formation. **METHODS:** An extensive review was made (e.g., using PubMed, Science Direct, and Web of Knowledge) of the literature. **RESULTS:** Melatonin, which is released into the saliva, may have important implications for dental disorders, especially in periodontal disease. Diseases of the periodontium are known to be aggravated by free radicals and by alterations in the immune response to microorganisms that are present in plaque. In response to periodontal inflammation, the blood and salivary levels of melatonin may increase. **CONCLUSION:** Melatonin may play a role in protecting the oral cavity from tissue damage that is due to oxidative stress, and it may contribute to the regeneration of alveolar bone through the stimulation of type I collagen fiber production and the modulation of osteoblastic and osteoclastic activity.

J Periodontol. 2007 Jun;78(6):1094-102

### **COMPARATIVE STUDY OF THE EFFECTS OF MELATONIN AND EPITALON ON THE PROTRACTED MEMORY UNDER THE SHUTTLE LABYRINTH TEST CONDITIONS IN RATS IN THE COURSE OF AGING.**

The influence of the chronic administration of melatonin (epiphyseal hormone) and epitalon (a synthetic tetrapeptide increasing melatonin production) on the learning process and the protracted memory has been studied in LIO rats in the course of aging for 2 years under standard illumination regime (12L :12D). The daily administration of melatonin (Sigma, USA) with drinking water (in 10 mg/liter dose at night) in rats beginning with the age of 4 months did not influence the learning processes in young and adult animals but it was found to contribute to optimization of the brain cognitive function in rats in the course of aging, by improving the protracted memory process. Epitalon administered in a daily dose of 0.1 microg per animal beginning with the age of 4 months showed mnemotropic properties (decreasing the extent of memory disorders) in old rats under conditions of the shuttle labyrinth test.

Eksp Klin Farmakol. 2006 Nov-Dec;69(6):13-6

## **BIOCHEMOTHERAPY WITH STANDARD CHEMOTHERAPIES PLUS THE PINEAL HORMONE MELATONIN IN THE TREATMENT OF ADVANCED SOLID NEOPLASMS.**

It is known since many years that the pineal hormone melatonin (MLT) may play anticancer activity through several mechanisms, including antiproliferative and immunostimulating effects. Moreover, it exerts an important antioxidant action. Therefore, MLT could be useful in the treatment of human neoplasms, either alone or in association with chemotherapy. The present study was performed to evaluate the influence of a concomitant MLT administration on efficacy and toxicity of several chemotherapeutic combinations in metastatic solid tumor patients, suffering from non-small cell lung cancer (NSCLC) or gastrointestinal tumors. The study included 370 patients who were randomized to receive chemotherapy alone or chemotherapy plus MLT (20 mg/day orally in the evening every day). NSCLC patients received cisplatin (CDDP) plus etoposide or CDDP plus gemcitabine. Colorectal cancer patients were treated with oxaliplatin plus 5-fluorouracil (5-FU), or weekly CPT-11 or 5-FU and folates (FA). Finally, gastric cancer patients received CDDP, epirubicin, 5-FU and FA or weekly 5-FU plus FA. The overall tumor regression rate achieved in patients concomitantly treated with MLT was significantly higher than that found in those treated with chemotherapy alone. Moreover, the 2-year survival rate was significantly higher in patients concomitantly treated with MLT. These results confirm in human the anticancer therapeutic properties of the pineal hormone MLT, which may enhance the efficacy of the standard anticancer chemotherapies.

Pathol Biol (Paris). 2007 Apr-May;55 (3-4):201-4

## **DELAYED MELATONIN ADMINISTRATION PROMOTES NEURONAL SURVIVAL, NEUROGENESIS AND MOTOR RECOVERY, AND ATTENUATES HYPERACTIVITY AND ANXIETY AFTER MILD FOCAL CEREBRAL ISCHEMIA IN MICE.**

Melatonin is a potent antioxidant with neuroprotective activity in animal models of ischemic stroke, which based on its lack of serious toxicity has raised hopes that it might be used for human stroke treatment in the future. This study investigated how subacute delivery of melatonin, starting at 24 hr after stroke onset, and continuing for 29 days (4 mg/kg/day; via drinking water), influences neuronal survival, endogenous neurogenesis, motor recovery and locomotor activity in C57Bl6/j mice submitted to 30-min middle cerebral artery occlusion. Histologic studies showed that melatonin improved neuronal survival and enhanced neurogenesis, even when applied 1 day after stroke. Cell survival was associated with a long-lasting improvement of motor and coordination deficits, evaluated by the grip strength and RotaRod tests, as well as with attenuation of hyperactivity and anxiety of the animals as revealed in open field tests. The robust functional neurologic improvements encourage proof-of-concept studies with melatonin in human stroke patients.

J Pineal Res. 2008 Feb 14

## **EFFECT OF PINEALECTOMY AND MELATONIN REPLACEMENT ON MORPHOLOGICAL AND BIOCHEMICAL RECOVERY AFTER TRAUMATIC BRAIN INJURY.**

Numerous studies showed that melatonin, a free radical scavenger, is neuroprotective. In this study, we investigated the effect of pinealectomy and administration of exogenous melatonin on oxidative stress and morphological changes after experimental brain injury. The animals were divided into six groups, each having 12 rats. Group 1 underwent craniotomy alone. Group 2 underwent craniotomy followed by brain trauma and received no medication. Group 3 underwent craniotomy followed by brain trauma and received melatonin. Group 4 underwent pinealectomy and craniotomy alone. Group 5 underwent pinealectomy and craniotomy followed by brain injury and received no medication. Group 6 underwent pinealectomy and craniotomy followed by brain trauma and received melatonin. Melatonin (100 mg/kg) was given intraperitoneally immediately after trauma to the rats in Groups 3 and 6. Pinealectomy caused a significant increase in the malondialdehyde (MDA), nitric oxide (NO), glutathione (GSH), and xanthine oxidase (XO) levels, and a decrease in GSH levels as compared to the control group. Trauma to pinealectomized rats causes significantly higher oxidative stress. Exogenous melatonin administration significantly reduced MDA, XO and NO levels, increased GSH levels, and attenuated tissue lesion area. These findings suggest that reduction in endogenous melatonin after pinealectomy makes the rats more vulnerable to trauma, and exogenous melatonin administration has an important neuroprotective effect.

Int J Dev Neurosci. 2006 Oct;24(6):357-63.

## **BLOOD PRESSURE MODULATION AND CARDIOVASCULAR PROTECTION BY MELATONIN: POTENTIAL MECHANISMS BEHIND.**

The production of the pineal hormone melatonin is synchronized with day-night cycle via multisynaptic pathway including suprachiasmatic nucleus linking several physiological functions to diurnal cycle. The recent data indicate that impaired melatonin production is involved in several cardiovascular pathologies including hypertension and ischemic heart disease. However, the mechanisms of melatonin effect on cardiovascular system are still not completely understood. The activation of melatonin receptors on endothelial and vascular smooth muscle cells and antioxidant properties of melatonin could be responsible for the

melatonin effects on vascular tone. However, the data from in vitro studies are controversial making the explanation of the melatonin effect on blood pressure in vivo difficult. In vivo, melatonin also attenuates sympathetic tone by direct activation of melatonin receptors, scavenging free radicals or increasing NO availability in the central nervous system. The central and peripheral antiadrenergic action of chronic melatonin treatment might eliminate the mechanisms counter-regulating decreased blood pressure, providing thus additional cardioprotective mechanism. The extraordinary antioxidant activity and antilipidemic effects of melatonin may enhance the modulation of blood pressure by melatonin and probably play the most important role in the amelioration of target organ damage by chronic melatonin treatment. Further investigation of these mechanisms should provide novel knowledge about pathophysiological mechanisms of cardiovascular diseases, additional explanation for their circadian and seasonal variability and potentially generate new impulses for the development of therapeutic arsenal.

Physiol Res. 2007;56(6):671-84.

### **MELATONIN AS MODULATOR OF PANCREATIC ENZYME SECRETION AND PANCREATOPROTECTOR.**

Melatonin, the main product of the pineal gland, is also released from the gastrointestinal endocrine-neurocrine (EE) cells. The concentrations of melatonin produced in the gut exceeds that originating from central nervous system. In spite of the presence of melatonin receptors in the pancreatic tissue little is known about the role of this indole in the pancreas. Our experimental studies have shown that exogenous melatonin, as well as this produced endogenously from its precursor; L-tryptophan, strongly stimulates pancreatic amylase secretion when given intraperitoneally, or into the gut lumen. This was accompanied by significant increases of CCK plasma level. Above pancreatostimulatory effects of luminal administration of melatonin, were completely reversed by bilateral vagotomy, capsaicin deactivation of sensory nerves or pretreatment of the rats with CCK1 receptor antagonist; tarazepide as well as serotonin antagonist; ketanserin. Melatonin, as well as its precursor; L-tryptophan, effectively protects the pancreas against the damage induced by caerulein overstimulation or ischemia/reperfusion. The beneficial effects of melatonin or L-tryptophan on acute pancreatitis could be related to the ability of melatonin to scavenge the free radicals, to activate antioxidative enzymes and to modulate the cytokine production.

J Physiol Pharmacol. 2007 Dec;58 Suppl 6:65-80

### **ROLE OF INSULIN RESISTANCE AND HYPERGLYCEMIA IN THE DEVELOPMENT OF ATHEROSCLEROSIS.**

Insulin resistance (IR) is the underlying defect in >90% of patients with type 2 diabetes mellitus and the major pathologic mechanism for the associated susceptibility to premature cardiovascular disease (CVD). The progression of IR to diabetes parallels the progression of endothelial dysfunction to atherosclerosis. The downregulation of the antiatherogenic phosphatidylinositol-3-kinase-mediated insulin receptor-signaling pathway, and maintained activity of the proatherogenic mitogen-activated protein kinase pathway in insulin-resistant states, leads to accelerated atherosclerosis. Efforts to prevent or slow the epidemic of atherothrombotic CVD must focus on the reversal of the disturbances in glucose and lipid homeostasis through the amelioration of IR.

Am J Cardiol. 2007 Feb 19;99(4A):6B-14B

### **INFLAMMATORY BIOMARKERS AND RISKS OF MYOCARDIAL INFARCTION, STROKE, DIABETES, AND TOTAL MORTALITY: IMPLICATIONS FOR LONGEVITY.**

Inflammation is recognized as a major etiologic determinant of multiple disease states including myocardial infarction, stroke, diabetes, and metabolic syndrome, and individuals with elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) are at increased risk of mortality and morbidity from these conditions. Novel screening algorithms, such as the Reynolds Risk Score, that incorporate inflammation can greatly improve risk detection in primary prevention. In high-risk secondary prevention settings such as acute coronary syndrome patients being treated with statin therapy, achieving low levels of plasma hsCRP concentration appears to be of similar importance as achieving low levels of LDL cholesterol. Whether inflammation in general or CRP in particular are appropriate targets for therapy remains controversial and is under investigation. Several novel methods to reduce CRP have been proposed, including direct inhibitors as well as antisense technologies.

Nutr Rev. 2007 Dec;65(12 Pt 2):S253-9

### **INFLAMMATION, INSULIN RESISTANCE, AND OBESITY.**

Obesity, in particular visceral obesity, has strong associations with cardiovascular disease and is related to many factors that are constituents of the metabolic syndrome. Increasing evidence suggests that features of the metabolic syndrome, including visceral obesity, are associated with a low-grade inflammatory state. Indeed, visceral fat is a source of several molecules, such as leptin, adiponectin, tumor necrosis factor-alpha, and interleukin 6, that are collectively called adipokines. All of them may induce a proinflammatory state and oxidative damage, leading to initiation and progression of atherosclerosis. Reduced-energy diets might represent an effective and healthful approach for long-term weight loss in patients with metabolic syndrome by reducing the underlying inflammatory condition.

Curr Atheroscler Rep. 2004 Nov;6(6):424-31

### **EFFECT OF DHEA ON ABDOMINAL FAT AND INSULIN ACTION IN ELDERLY WOMEN AND MEN: A RANDOMIZED CONTROLLED TRIAL.**

CONTEXT: Dehydroepiandrosterone (DHEA) administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance in laboratory animals, but it is not known whether DHEA decreases abdominal obesity in humans. DHEA is widely available as a dietary supplement without a prescription. OBJECTIVE: To determine whether DHEA replacement therapy decreases abdominal fat and improves insulin action in elderly persons. DESIGN AND SETTING: Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from June 2001 to February 2004. PARTICIPANTS: Fifty-six elderly persons (28 women and 28 men aged 71 [range, 65-78] years) with age-related decrease in DHEA level. INTERVENTION: Participants were randomly assigned to receive 50 mg/d of DHEA or matching placebo for 6 months. MAIN OUTCOME MEASURES: The primary outcome measures were 6-month change in visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test (OGTT). RESULTS: Of the 56 men and women enrolled, 52 underwent follow-up evaluations. Compliance with the intervention was 97% in the DHEA group and 95% in the placebo group. Based on intention-to-treat analyses, DHEA therapy compared with placebo induced significant decreases in visceral fat area (-13 cm<sup>2</sup> vs +3 cm<sup>2</sup>, respectively; P = .001) and

subcutaneous fat (-13 cm<sup>2</sup> vs +2 cm<sup>2</sup>, P = .003). The insulin area under the curve (AUC) during the OGTT was significantly reduced after 6 months of DHEA therapy compared with placebo (-1119 muU/mL per 2 hours vs +818 muU/mL per 2 hours, P = .007). Despite the lower insulin levels, the glucose AUC was unchanged, resulting in a significant increase in an insulin sensitivity index in response to DHEA compared with placebo (+1.4 vs -0.7, P = .005). CONCLUSION: DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity.

JAMA. 2004 Nov 10;292(18):2243-8

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