22. Osteoporosis

Preventative and curative options include:

Calcium. magnesium, zinc, manganese, vitamin D3, DHEA, soy extract, ipriflavone, progesterone cream, vitamin K, GLA/DHA, fish oil

Efficacy of ipriflavone in established osteoporosis and long-term safety.

Agnusdei D, Bufalino L. Institute of Internal Medicine and Medical Pathology, University of Siena, Italy.

Calcif Tissue Int 1997;61 Suppl 1:S23-7

Ipriflavone (i.p.), an isoflavone derivative, is currently used in several countries for prevention and treatment of osteoporosis. Recently, 149 elderly, osteoporotic women (65-79 years) with prevalent vertebral fractures were enrolled in two Italian, multicenter, double-blind, 2-year studies. Women were randomly allocated to receive either oral i.p. (200 mg T.I.D. at meals) or matching placebo, plus 1 g oral calcium daily. One hundred eleven subjects completed the 2-year treatment period. A significant increase in forearm bone mineral density (BMD), measured by dual photon absorptiometry (DPA), was obtained after i.p. treatment. Women receiving the placebo showed only a limited bone loss during the treatment period, probably due to calcium supplement; however, a significant between-treatment difference was obtained in both studies. Urinary hydroxyproline was significantly decreased in i.p.-treated patients, suggesting a reduction in bone turnover rate. A reduction of incident vertebral fractures was observed in i.p.-treated women compared with control subjects. A significant improvement of bone pain and mobility has also been pointed out in one of the studies. To date, 2769 patients have been treated with i.p., for a total of 3132 patient/years, in 60 clinical studies performed in Italy, Japan, and Hungary and reviewed for long-term safety assessment. The incidence of adverse reactions in ipriflavone-treated patients (14.5%) was similar to that observed in subjects receiving the placebo (16.1%). Side effects were mainly gastrointestinal. Few patients presented reversible modifications of laboratory parameters. The data from the above studies show that long-term treatment with i.p. may be considered safe, and may increase bone density and possibly prevent fractures in elderly patients with established osteoporosis.

Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial.

Alexandersen P, Toussaint A, Christiansen C, Devogelaer JP, Roux C, Fechtenbaum J, Gennari C, Reginster JY; Ipriflavone Multicenter European Fracture Study. Center for Clinical and Basic Research, Ballerup Byvej 222, 2750 Ballerup, Denmark. pa@ccbr.dk

JAMA 2001 Mar 21;285(11):1482-8

CONTEXT: Data on the efficacy and safety of ipriflavone for prevention of postmenopausal bone loss are conflicting. OBJECTIVES: To investigate the effect of oral ipriflavone on prevention of postmenopausal bone loss and to assess the safety profile of long-term treatment with ipriflavone in postmenopausal osteoporotic women. DESIGN AND SETTING: Prospective, randomized, double-blind, placebo-controlled, 4-year study conducted in 4 centers in Belgium, Denmark, and Italy from August 1994 to July 1998. PARTICIPANTS: Four hundred seventy-four postmenopausal white women, aged 45 to 75 years, with bone mineral densities (BMDs) of less than 0.86 g/cm(2). INTERVENTIONS: Patients were randomly assigned to receive ipriflavone, 200 mg 3 times per day (n = 234), or placebo (n = 240); all received 500 mg/d of calcium. MAIN OUTCOME MEASURES: Efficacy measures included spine, hip, and forearm BMD and biochemical markers of bone resorption (urinary hydroxyproline corrected for creatinine and urinary CrossLaps [Osteometer Biotech, Herlev, Denmark] corrected for creatinine), assessed every 6 months. Laboratory safety measures and adverse events were recorded every 3 months. RESULTS: Based on intent-to-treat analysis, after 36 months of treatment, the annual percentage change from baseline in BMD of the lumbar spine for ipriflavone vs placebo (0.1% [95% confidence interval (CI), -7.9% to 8.1%] vs 0.8% [95% CI, -9.1% to 10.7%]; P =.14), or in any of the other sites measured, did not differ significantly between groups. The response in biochemical markers was also similar between groups (eg, for hydroxyproline corrected for creatinine, 20.13 mg/g [95% CI, 18.85-21.41 mg/g] vs 20.67 mg/g [95% CI, 19.41-21.92 mg/g]; P =.96); urinary CrossLaps corrected for creatinine, 268 mg/mol (95% CI, 249-288 mg/mol) vs 268 mg/mol (95% CI, 254-282 mg/mol); P =.81. The number of women with new vertebral fracture was identical or nearly so in the 2 groups at all time points. Lymphocyte concentrations decreased significantly (500/microL (0.5 x 10(9)/L]) in women treated with ipriflavone. Thirty-one women (13.2%) in the ipriflavone group developed subclinical lymphocytopenia, of whom 29 developed it during ipriflavone treatment. Of these, 15 (52%) of 29 had recovered spontaneously by 1 year and 22 (81%) of 29 by 2 years. CONCLUSIONS: Our data indicate that ipriflavone does not prevent bone loss or affect biochemical markers of bone metabolism. Additionally, ipriflavone induces lymphocytopenia in a significant number of women.

Beverage choices affect adequacy of children's nutrient intakes.

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Arch Pediatr Adolesc Med 2000 Nov;154(11):1148-52

OBJECTIVE: To assess the relationship between beverage choices and the adequacy of nutrient intakes among children and adolescents. DESIGN: Beverages reported in 24-hour recall records were classified as milk, 100% juice, fruit-flavored drinks, or carbonated sodas. Recommended intakes were based on

Recommended Dietary Allowances or Dietary Reference Intakes. PARTICIPANTS: Four thousand seventy children aged 2 to 5, 6 to 11, and 12 to 17 years participating in the 1994-96 Continuing Survey of Food Intakes by Individuals. STATISTICAL ANALYSIS: The likelihood of achieving recommended intakes of selected nutrients on the day of recall was assessed with multiple logistic regression including ounces of milk, juice, fruit-flavored drinks, and carbonated sodas in the model while controlling for sex, age in years, race/ethnic group, household income, and total energy intake. RESULTS: Milk consumption was positively (P<.0001) associated with the likelihood of achieving recommended vitamin A, folate, vitamin B(12), calcium, and magnesium intakes in all age strata. Juice consumption was positively (P< or =. 001) associated with achieving recommended vitamin C and folate intakes in all age strata and magnesium intakes among children aged 6 years and older. Carbonated soda consumption was negatively (P< or =. 01) associated with achieving vitamin A intake in all age strata, calcium in children younger than 12 years, and magnesium in children aged 6 years and older. CONCLUSION: Beverage choice can have a significant effect on the nutrient adequacy of the diets of children and adolescents.

Management of osteoporosis. An overview.

Castelo-Branco C. Department of Gynaecology & Obstetrics, IDIBAPS (Institut d'Investigacio Biomedica Agusti Pi Sunyer), Hospital Clinic i Provincial, School of Medicine, University of Barcelona, Spain.

Drugs Aging (New Zealand) 1998, 12 Suppl 1 p25-32

Osteoporosis is a common disease associated with aging and menopause, and is becoming a major health and socioeconomic problem worldwide. The 2 major determinants of risk of osteoporosis are peak bone mass (reached in the third decade of life) and bone loss thereafter. There is substantial evidence that bone mass is of major importance for the strength of bone and the risk of fracture. The measurement of bone mass in the third decade of life is therefore a potentially useful tool in assessing the individual risk of fracture. Moreover, biochemical markers of bone formation and resorption may be of some use in predicting oss and the response to therapy. Since the most well-defined risk factor for osteoporosis is the cessation of ovarian estrogen production at menopause, estrogen replacement therapy (ERT) is the treatment of choice for postmenopausal bone loss. While the benefits of ERT in preventing bone loss and reducing the incidence of fractures are well established, such therapy is contraindicated in some women and is not an acceptable option for others. Other widely used treatments for osteoporosis that have been utilised to prevent bone loss include calcitonin and bisphosphonates, calcium supplementation, ossein-hydroxyapatite compound, vitamin D analogues, sodium fluoride, parathyroid hormone, anabolic steroids and growth hormone. While ERT is presently the best option for the prevention of bone loss, a regimen of ERT combined with lifestyle changes (e.g., exercise and diet) as well as other bone-preserving drugs may increase bone mass in postmenopausal women to a greater extent than ERT alone (44 references).

Improved bone metabolism in female elite athletes after vitamin K supplementation.

Craciun AM, Wolf J, Knapen MH, Brouns F, Vermeer C. Department of Biochemistry and Cardiovascular Research Institute, Maastricht University, The Netherlands.

Int J Sports Med 1998 Oct;19(7):479-84

In female elite athletes strenuous exercise may result in hypoestrogenism and amenorrhoea. As a consequence, a low peak bone mass and rapid bone loss are often seen in relatively young athletes. In postmenopausal women, increased intake of vitamin K may result in an increase of serum markers for bone formation, a decrease of urinary markers for bone resorption, and a decrease in urinary calcium loss. In the present paper we report an intervention study among eight female athletes, four of whom had been amenorrhoeic for more than one year, whereas the others had been using oral contraceptives. All participants received vitamin K supplementation (10 mg/day) during one month, and various bone markers were measured before and after treatment. At baseline the athletes not using oral contraceptives were biochemically vitamin K-deficient as deduced from the calcium binding capacity of the circulating bone protein osteocalcin. In all subjects increased vitamin K was associated with an increased calcium-binding capacity of osteocalcin. In the low-estrogen group vitamin K supplementation induced a 15-20% increase of bone formation markers and a parallel 20-25% decrease of bone resorption markers. This shift is suggestive for an improved balance between bone formation and resorption.

Daily oral magnesium supplementation suppresses bone turnover in young adult males.

Dimai HP, Porta S, Wirnsberger G, Lindschinger M, Pamperl I, Dobnig H, Wilders-Truschnig M, Lau KH. Department of Endocrinology, University of Graz Medical School, Austria.

J Clin Endocrinol Metab (United States) Aug 1998, 83 (8) p2742-8

This study examined the effects of daily oral magnesium (Mg) supplementation on bone turnover in 12 young (27-36 yr old) healthy men. Twelve healthy men of matching age, height, and weight were recruited as the control group. The study group received orally 15 mmol Mg (Magnosolv powder, Asta Medica) daily in the early afternoon with 2-h fasting before and after Mg intake. Fasting blood and second void urine samples were collected in the early morning on days 0, 1, 5, 10, 20, and 30, respectively. Total and ionized Mg2+ and calcium (Ca2+), and intact PTH (iPTH) levels were determined in blood samples. Serum biochemical markers of bone formation (i.e. C-terminus of type I procollagen peptide and osteocalcin) and resorption (i.e. type I collagen telopeptide) and urinary Mg level adjusted for creatinine were measured. In these young males, 30 consecutive days of oral Mg supplementation had no significant effect on total circulating Mg level, but caused a significant reduction in the serum ionized Mg+ level after 5 days of

intake. The Mg supplementation also significantly reduced the serum iPTH level, which did not appear to be related to changes in serum Ca2+ because the Mg intake had no significant effect on serum levels of either to tal or ionized Ca2+. There was a strong positive correlation between serum iPTH and ionized Mg2+ ($r = 0.699$; $P < 0.001$), supporting the contention that decreased serum iPTH may be associated with the reduction in serum ionized Mg2+. Mg supplementation also reduced levels of both serum bone formation and resorption biochemical markers after 1-5 days, consistent with the premise that Mg supplementation may have a suppressive effect on bone turnover rate. Covariance analyses revealed that serum bone formation markers correlated negatively with ionized Mg2+ ($r = -0.274$ for type I procollagen peptide and -0.315 for osteocalcin), but not with iPTH or ionized Ca2+. Thus, the suppressive effect on bone formation may be mediated by the reduction in serum ionized Mg2+ level (and not iPTH or ionized Ca2+). In summary, this study has demonstrated for the first time that oral Mg supplementation in normal young adults caused reductions in serum levels of iPTH, ionized Mg2+, and biochemical markers of bone turnover. In conclusion, oral Mg supplementation may suppress bone turnover in young adults. Because increased bone turnover has been implicated as a significant etiological factor for bone loss, these findings raise the interesting possibility that oral Mg supplementation may have beneficial effects in reducing bone loss associated with high bone turnover, such as age-related osteoporosis.

Vitamin K intake and hip fractures in women: a prospective study.

Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. diane.feskanich@channing.harvard.edu

Am J Clin Nutr 1999 Jan;69(1):74-9

BACKGROUND: Vitamin K mediates the gamma-carboxylation of glutamyl residues on several bone proteins, notably osteocalcin. High serum concentrations of undercarboxylated osteocalcin and low serum concentrations of vitamin K are associated with lower bone mineral density and increased risk of hip fracture. However, data are limited on the effects of dietary vitamin K. OBJECTIVE: We investigated the hypothesis that high intakes of vitamin K are associated with a lower risk of hip fracture in women. DESIGN: We conducted a prospective analysis within the Nurses' Health Study cohort. Diet was assessed in 72327 women aged 38-63 y with a food-frequency questionnaire in 1984 (baseline). During the subsequent 10 y of follow-up, 270 hip fractures resulting from low or moderate trauma were reported. RESULTS: Women in quintiles 2-5 of vitamin K intake had a significantly lower age-adjusted relative risk (RR: 0.70; 95% CI: 0.53, 0.93) of hip fracture than women in the lowest quintile (< 109 microg/d). Risk did not decrease between quintiles 2 and 5 and risk estimates were not altered when other risk factors for osteoporosis, including calcium and vitamin D intakes, were added to the models. Risk of hip fracture was also inversely associated with lettuce consumption (RR: 0.55; 95% CI: 0.40, 0.78) for one or more servings per day compared with one or fewer servings per week), the food that contributed the most to dietary vitamin K intakes. CONCLUSIONS: Low

intakes of vitamin K may increase the risk of hip fracture in women. The data support the suggestion for a reassessment of the vitamin K requirements that are based on bone health and blood coagulation.

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; Isaia G; Mazzuoli G; Ortolani S; Bufalino L; Passeri M. Internal Medicine and Medical Pathology Institute, University of Siena, Italy.

Menopause (United States) Spring 1998, 5 (1) p9-15

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 (-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.

Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and IL-6 levels in women.

Haden ST, Glowacki J, Hurwitz S, Rosen C, LeBoff MS. Endocrine-Hypertension Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, Massachusetts 02115, USA.

Calcif Tissue Int 2000 Jun;66(6):414-8

Data from animal and in vitro studies suggest that the growth-promoting effects of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) may be mediated by stimulation of insulin-like growth factor-I (IGF-I) and/or inhibition of interleukin 6 (IL-6), a cytokine mediator of bone resorption. This study tests the hypotheses that there are effects of age on serum DHEAS, IGF-I, and IL-6 levels, and that levels of IGF-I and IL-6 are related to DHEAS levels. The study included 102 women: 27 premenopausal and 75 postmenopausal, including 35 postmenopausal women with osteoporosis, as defined by bone mineral density scores by dual X-ray energy absorptiometry. DHEAS levels decreased significantly with age ($r = -0.52$, $P < 0.0001$) and IGF-I levels decreased

significantly with age (r = -0.49, P < 0.0001). IL-6 levels increased significantly with age (r = 0.36, P = 0.008). IGF-I was positively correlated to DHEAS levels (r = 0.43, P < 0. 0001, n = 102) and IL-6 levels were negatively correlated to DHEAS levels (r = -0.32, P = 0.021, n = 54). Levels of DHEAS and IGF-I were correlated with T scores of the spine and some hip sites. In a multiple variable model to predict DHEAS, age was an important predictor (P < 0.001), but osteoporosis status, IGF-I, and IL-6 were not. The median DHEAS level was lower in the postmenopausal osteoporotic women (67 microg/dl, n = 35) than in the nonosteoporotic postmenopausal women (106.3 microg/dl, n = 40, P = 0. 03), but this was not significant after correction for age. Age accounted for 32% of the variance in DHEAS levels. In summary, DHEAS levels decreased with age and had a positive association with IGF-I levels and a negative association with IL-6 levels. DHEA deficiency may contribute to age-related bone loss through anabolic (IGF-I) and anti-osteolytic (IL-6) mechanisms.

The effect of an ipriflavone-containing supplement on urinary N-linked telopeptide levels in postmenopausal women.

Halpner AD, Kellermann G, Ahlgrimm MJ, Arndt CL, Shaikh NA, Hargrave JJ, Tallas PG. Douglas Laboratories, Pittsburgh, Pennsylvania 15205, USA.

J Womens Health Gend Based Med 2000 Nov;9(9):995-8

Osteoporosis is a significant health concern to our aging population. We report here the results of a pilot placebo-controlled trial of a dietary supplement containing ipriflavone, calcium, and vitamin D on a urinary marker of bone breakdown in postmenopausal women. Seven postmenopausal women not currently receiving hormone replacement therapy received either an ipriflavone-containing supplement or placebo for 3 months. Urinary N-linked telopeptides, a marker of bone breakdown, declined by 29% in those receiving the supplement, whereas an increase in this marker was observed in the group receiving the placebo. No changes were observed in salivary hormone measurements. Although our sample size was small, to the best of our knowledge, this is the first report that demonstrates changes in N-linked telopeptide levels as a result of consuming an ipriflavone-containing product. Our findings confirm those of other researchers that demonstrate the usefulness of ipriflavone at slowing the progression of bone loss and suggest that measuring N-linked telopeptides may be a useful tool to assess therapeutic efficacy.

IL-6, DHEA and the ageing process.

James K, Premchand N, Skibinska A, Skibinski G, Nicol M, Mason JI. Department of Surgery, University of Edinburgh Medical School, UK.

Mech Ageing Dev 1997 Feb;93(1-3):15-24

The age-related increase in circulating IL-6 levels in humans which has been attributed to a decline in DHEA production by the adrenal gland is currently attracting attention because of its possible relevance to the aetiology and

management of a number of age-related clinical disorders. The potential importance of these observations and suggestions has prompted us to perform more detailed studies on the relationship between IL-6 and DHEA. Using immunoassay techniques we have found in normal healthy individuals over the age of 40 an inverse relationship between plasma DHEA levels and the presence of detectable levels of IL-6 (more than 1 pg/ml). In vitro, studies also revealed that low dose (10(-6)-10(-8) M) of DHEA and DHEAS inhibited the production of IL-6 in unstimulated human spleen cell suspension cultures whilst enhancing its release by explant cultures of the same tissue. In contrast they had no effect on immunoglobulin production. These studies suggest that there is a real, but complex relationship between IL-6 production and DHEA levels which warrants further investigation.

The effect of vitamin K supplementation on circulating osteocalcin (bone Gla protein) and urinary calcium excretion.

Knapen MH, Hamulyak K, Vermeer C. University of Limburg, Maastricht, The Netherlands.

Ann Intern Med 1989 Dec 15;111(12):1001-5

STUDY OBJECTIVE: To determine whether vitamin K administration affects urinary calcium excretion in postmenopausal women. DESIGN: Before- and after-trials with a 2-week treatment period. SUBJECTS: Healthy postmenopausal women (55 to 75 years old) were recruited from the convents in and around Maastricht. Controls (25 to 40 years old) were healthy premenopausal volunteers. INTERVENTION: Daily administration of 1 mg of vitamin K for 2 weeks. MEASUREMENTS: Serum immunoreactive osteocalcin: hydroxylapatite binding (HAB) capacity of serum immunoreactive osteocalcin; excretion of calcium, hydroxyproline, and creatinine in the urine during the last 2 h of a 16-h fasting period. RESULTS: In premenopausal women, no effect of vitamin K administration was seen. In the postmenopausal group, vitamin K induced increased serum immunoreactive osteocalcin concentration; normalization of the HAB capacity of serum immunoreactive osteocalcin (this marker was less than 50% that of the controls in the pretreatment samples); a decrease in urinary calcium excretion, notably in the "fast losers" of calcium; and a parallel decrease in urinary hydroxyproline excretion in the fast losers of calcium. CONCLUSIONS: The serum immunoreactive osteocalcin level may vary with vitamin K status. This variance should be taken into consideration if osteocalcin is used as a marker for osteoblast activity. Vitamin K is one factor that may play a role in the loss of bone mass in postmenopausal osteoporosis.

Vitamin K-induced changes in markers for osteoblast activity and urinary calcium loss.

Knapen MH, Jie KS, Hamulyak K, Vermeer C. Department of Biochemistry, University of Limburg, Maastricht, The Netherlands.

Calcif Tissue Int 1993 Aug;53(2):81-5

The objective of this study was to identify subjects in whom vitamin K has an effect on markers for calcium and bone metabolism and to detect hitherto-unnoticed correlations between vitamin K-induced changes in these markers. Participants in our studies were apparently healthy women, in whom we measured serum-immunoreactive osteocalcin (irOC) before and after adsorption to hydroxylapatite; total serum alkaline phosphatase (T-AP) and bone-specific alkaline phosphatase (B-AP); and fasting urinary calcium and creatinine. We describe a trial among 145 women who were treated with vitamin K (1 mg/day) for 2 weeks, and a prospective placebo-controlled trial among two groups each of 70 postmenopausal women with a treatment period of 3 months. It turned out that in elderly women vitamin K induced increased levels of serum irOC with a high affinity for hydroxylapatite (irOCbound), whereas that with low affinity (irOCfree) remained unaffected. In placebo-treated women the ratio irOCfree/irOCbound shifted from 0.38 to 0.65 around the 50th year of age. This shift was not found in vitamin K-treated women. After 3 months of treatment the vitamin K-induced changes in irOCbound were correlated with changes in B-AP, whereas irOCfree was correlated to urinary calcium excretion. In fast losers of urinary calcium vitamin K induced a 30% decrease of calcium excretion. The hypothesis is put forward that irOCbound may be a marker for bone formation, that serum irOCfree may be a marker for bone resorption, and that the serum irOCfree/irOCbound ratio may become a marker for skeletal remodeling. (ABSTRACT TRUNCATED AT 250 WORDS.)

[New spine and non-spine fractures in 871 women/year treated with oral pamidronate plus calcium and vitamin D supplements.] [Article in Spanish]

Man Z, Otero AB. Centro de Endocrinologia T.I.E.M.P.O., Buenos Aires, Argentina.

Medicina (B Aires) 1997;57 Suppl 1:32-6

A sample of 871.3 patients/year was conformed by 205 postmenopausal women, aged 64.8 +/- 18.2 years (mean +/- SD), followed up during 51 +/- 12 months. All have osteoporosis, diagnosis assessed through radiological findings of at least one atraumatic fracture or vertebral crush ("severe osteoporosis" according to the new WHO classification). Each woman received 100 mg/day oral pamidronate (enteric coated soft gelatin capsules), half an hour before breakfast. Additional calcium and vitamin D were supplemented as follows: Total daily calcium = 1 g provided by diet and/or calcium carbonate. Vitamin D equivalent to 400-1200 IU/day. All patients were recommended to improve their physical activity, at least by walking exercise. Clinical examination radiological, bone mineral density (BMD) and biochemical studies were periodically performed. But, fracture indicence was the end-point of the study. Same was related to the 1,673 fall episodes recorded in the sample. In addition, height loss, lumbar BMD, proximal femur BMD, are also reported. Data has been cross-sectional collected in March 1995. All patients improved the symptomatology, specifically pain. This, and the good tolerability of the treatments proved to be considerably favorable for their compliance. Within the observation period, only 12 patients decreased their height (5.85%; mean = 0.85 cm; range = 0.5-2.0 cm). Lumbar spine BMD increased in 90% of 48

women. Mean gain after 2 years was 5.3 +/- 1.0% ($p < 0.001$). Proximal femur increased in 78% of other 32 women. Mean gain 6.3 +/- 0.7% ($p < 0.001$) after 2 years. A total of 78 new fractures were recorded, 47 vertebral crush, 29 forearm fractures and 2 hip fractures. Its incidence related to the fall episodes was of 2.8; 1.7 and 0.12% respectively. When compared with a historical estimated data, from an untreated population (Cummings SR et al, 1994), both, the total number of new fractures and the new hip fractures were significantly lower ($p < 0.01$) in our treated population than the reference data. Pamidronate, in oral doses of 100 mg/day, adequately supplemented with calcium and vitamin D, proved to be effective and a well tolerated therapy. The low rate of height's loss, BMD significant increases in subgroups of patients and the low rate of new fractures, strongly support the use of the compound to treat severe osteoporotic women. To our knowledge, this is the first time, that the new fracture incidence is related to the fall frequency reported in a bisphosphonate treated sample.

Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women.

Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW Jr. Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, USA. spotter@protein.com

Am J Clin Nutr 1998 Dec;68(6 Suppl):1375S-1379S

The effects of soy protein (40 g/d) containing moderate and higher concentrations of isoflavones on blood lipid profiles, mononuclear cell LDL receptor messenger RNA, and bone mineral density and content were investigated in 66 free-living, hypercholesterolemic, postmenopausal women during a 6-mo, parallel-group, double-blind trial with 3 interventions. After a control period of 14 d, during which subjects followed a National Cholesterol Education Program Step I low-fat, low-cholesterol diet, all subjects were randomly assigned to 1 of 3 dietary groups: Step I diet with 40 g protein/d obtained from casein and nonfat dry milk (CNFDM), Step I diet with 40 g protein/d from isolated soy protein containing 1.39 mg isoflavones/g protein (ISP56), or Step I diet with 40 g protein/d from isolated soy protein containing 2.25 mg isoflavones/g protein (ISP90). Total and regional bone mineral content and density were assessed. Non-HDL cholesterol for both ISP56 and ISP90 groups was reduced compared with the CNFDM group ($P < 0.05$). HDL cholesterol increased in both ISP56 and ISP90 groups ($P < 0.05$). Mononuclear cell LDL receptor mRNA was increased in subjects consuming ISP56 or ISP90 compared with those consuming CNFDM ($P < 0.05$). Significant increases occurred in both bone mineral content and density in the lumbar spine but not elsewhere for the ISP90 group compared with the control group ($P < 0.05$). Intake of soy protein at both isoflavone concentrations for 6 mo may decrease the risk factors associated with cardiovascular disease in postmenopausal women. However, only the higher isoflavone-containing product protected against spinal bone loss.

Progesterone as a bone-trophic hormone.

Prior JC.

Endocr Rev 1990 May;11(2):386-98

Critical analysis of the reviewed data indicate that progesterone meets the necessary criteria to play a causal role in mineral metabolism. This review provides the preliminary basis for further molecular, genetic, experimental, and clinical investigation of the role(s) of progesterone in bone remodeling. Much further data are needed about the interrelationships between gonadal steroids and the "life cycle" of bone. Feldman et al., however, may have been prophetic when he commented; "If this anti-glucocorticoid effect of progesterone also holds true in bone, then postmenopausal osteoporosis may be, in part, a progesterone deficiency disease."

Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis.

Shiraki M, Shiraki Y, Aoki C, Miura M. Research Institute and Practice for Involutional Diseases, Nagano Prefecture, Japan.

J Bone Miner Res 2000 Mar;15(3):515-21

We attempted to investigate whether vitamin K2 (menatetrenone) treatment effectively prevents the incidence of new fractures in osteoporosis. A total of 241 osteoporotic patients were enrolled in a 24-month randomized open label study. The control group (without treatment; n = 121) and the vitamin K2-treated group (n = 120), which received 45 mg/day orally vitamin K2, were followed for lumbar bone mineral density (LBMD; measured by dual-energy X-ray absorptiometry [DXA]) and occurrence of new clinical fractures. Serum level of Glu-osteocalcin (Glu-OC) and menaquinone-4 levels were measured at the end of the follow-up period. Serum level of OC and urinary excretion of deoxypyridinoline (DPD) were measured before and after the treatment. The background data of these two groups were identical. The incidence of clinical fractures during the 2 years of treatment in the control was higher than the vitamin K2-treated group (chi2 = 10.935; p = 0.0273). The percentages of change from the initial value of LBMD at 6, 12, and 24 months after the initiation of the study were -1.8 +/- 0.6%, -2.4 +/- 0.7%, and -3.3 +/- 0.8% for the control group, and 1.4 +/- 0.7%, -0.1 +/- 0.6%, and -0.5 +/- 1.0% for the vitamin K2-treated group, respectively. The changes in LBMD at each time point were significantly different between the control and the treated group (p = 0.0010 for 6 months, p = 0.0153 for 12 months, and p = 0.0339 for 24 months). The serum levels of Glu-OC at the end of the observation period in the control and the treated group were 3.0 +/- 0.3 ng/ml and 1.6 +/- 0.1 ng/ml, respectively (p < 0.0001), while the serum level of OC measured by the conventional radioimmunoassay (RIA) showed a significant rise (42.4 +/-6.9% from the basal value) in the treated group at 24 months (18.2 +/- 6.1% for the controls;p = 0.0081). There was no significant change in urinary DPD excretion in the treated group. These findings suggest that vitamin K2 treatment effectively prevents the occurrence of new fractures, although the vitamin K2-treated group

failed to increase in LBMD. Furthermore, vitamin K2 treatment enhances gamma-carboxylation of the OC molecule.

Effect of recombinant human growth hormone in elderly osteoporotic women.

Sugimoto T, Nakaoka D, Nasu M, Kanzawa M, Sugishita T, Chihara K. Third Division, Department of Medicine, Kobe University School of Medicine, Kobe, Japan.

Clin Endocrinol (Oxf) 1999 Dec;51(6):715-24

OBJECTIVE: Bone mineral density and growth hormone (GH) secretion rate both decline during normal human ageing. We evaluated the effects of recombinant human GH on markers of body composition and bone turnover in an open study in 8 elderly osteoporotic women aged 68-75 years (mean age 71 years). DESIGN: Subjects were treated with GH as a single daily subcutaneous injection (0.125 IU/kg/week for the first 4 weeks and subsequently 0.25 IU/kg/week) for 48 weeks. RESULTS: GH treatment caused a rapid (within 2 weeks) increase in serum levels of IGF-I and IGF-binding protein-3 (IGFBP-3) which was sustained throughout the study. Markers of bone formation and resorption were both gradually increased up to 24 weeks of GH treatment. The bone formation markers, osteocalcin (OC) and bone alkaline phosphatase, remained high during GH treatment, while the bone resorption marker, deoxypyridinoline (D-Pyr), tended to return to baseline levels after 24 weeks of GH therapy. GH treatment for 48 weeks caused a significant increase in hand grip and a decrease in waist/hip ratio. The mean percentage changes in bone mineral density (BMD) of mid-radius and lumbar spine were + 2.1% and + 1.2%, respectively, although they were not statistically significant. GH treatment was well tolerated and no major side-effects except mild oedema and joint pain were found. Since GH treatment produced durable increases in bone formation markers, BMD continued to be monitored after discontinuation of GH treatment for another 48 weeks, during which significant increases in radial and lumbar BMD (8.1 +/- 2.1 and 3.8 +/- 1.4% above pre- treatment values, respectively) were recorded. CONCLUSION: These results indicate that GH attenuates the decrease in muscle strength and bone mass as well as the gain of abdominal fat with ageing in elderly women. The present data provide useful information about the application of GH treatment in elderly women.

Vitamin K and bone health.

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In the past decade it has become evident that vitamin K has a significant role to play in human health that is beyond its well-established function in blood clotting.

There is a consistent line of evidence in human epidemiologic and intervention studies that clearly demonstrates that vitamin K can improve bone health. The human intervention studies have demonstrated that vitamin K cannot only increase bone mineral density in osteoporotic people but also actually reduce fracture rates. Further, there is evidence in human intervention studies that vitamins K and D, a classic in bone metabolism, works synergistically on bone density. Most of these studies employed vitamin K(2) at rather high doses, a fact that has been criticized as a shortcoming of these studies. However, there is emerging evidence in human intervention studies that vitamin K(1) at a much lower dose may also benefit bone health, in particular when coadministered with vitamin D. Several mechanisms are suggested by which vitamin K can modulate bone metabolism. Besides the gamma-carboxylation of osteocalcin, a protein believed to be involved in bone mineralization, there is increasing evidence that vitamin K also positively affects calcium balance, a key mineral in bone metabolism. The Institute of Medicine recently has increased the dietary reference intakes of vitamin K to 90 microg/d for females and 120 microg/d for males, which is an increase of approximately 50% from previous recommendations.

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

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Menopause (United States) Spring 1998, 5 (1) p9-15

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 (-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.

Growth, development and differentiation: A functional food science approach

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British Journal of Nutrition (United Kingdom), 1998, 80/Suppl. 1 (S5-S45)

Few other aspects of food supply and metabolism are of greater biological importance than the feeding of mothers during pregnancy and lactation, and of their infants and young children. Nutritional factors during early development not only have short-term effects on growth, body composition and body functions but also exert long-term effects on ealth, disease and mortality risks in adulthood. as well as development of neural functions and behaviour, a phenomenon called 'metabolic programming'. The interaction of nutrients and gene expression may form the basis of many of these programming effects and needs to be investigated in more detail. The relation between availability of food ingredients and cell and tissue differentiation and its possible uses for promoting health and development requires further exploration. The course of pregnancy, childbirth and lactation as well as human milk composition and the short- and long term outcome of the child are influenced by the intake of foods and particularly micronutrients, e.g. polyunsaturated fatty acids, Fe, Zn and I. Folic acid supplementation from before conception through the first weeks of pregnancy can markedly reduce the occurrence of severe embryonic malformations; other potential benefits of modulating nutrient supply on maternal and child health should be further evaluated. The evaluation of dietary effects on child growth requires epidemiological and field studies as well as evaluation of specific cell and tissue growth. Novel substrates, growth factors and conditionally essential nutrients (e.g. growth factors, amino acids, polyunsaturated fatty acids) may be potentially useful redients in functional foods and need to be assessed carefully. Intestinal growth, maturation, and adaptation as well as long-term function may be influenced by food ingredients such as oligosaccharides, gangliosides, high-molecular-mass glycoproteins, bile salt-activated lipase, pre- and probiotics. There are indications for some beneficial effects of functional foods on the developing immune response, for example induced by antioxidant vitamins, trace elements, fatty acids, arginine, nucleotides, and altered antigen contents in infant foods. Peak bone mass at the end of adolescence can be increased by dietary means, which is expected to be of long-term importance for the prevention of osteoporosis at older ages. Future studies should be directed to the combined effects of Ca and other constituents of growing bone, such as P, Mg and Zn, as well as vitamins D and K, and the trace elements F and B. Pregnancy and the first postnatal months are critical time periods for the growth and development of the human nervous system, processes for which adequate substrate supplies are essential. Early diet seems to have long-term effects on sensory and cognitive abilities as well as behaviour. The potential beneficial effects of a balanced supply

of n Zn and polyunsaturated fatty acids should be further evaluated. Possible long-term effects of early exposure to tastes and flavours on later food choice preferences may have a major impact on public health and need to be further elucidated. The use of biotechnology and recombinant techniques may offer the opportunity to include various bioactive substances in special dietary products, such as human milk proteins, peptides, growth factors, which may have beneficial physiological effects, particularly in infancy and early childhood.

Osteoporosis in rheumatoid arthritis - Loss of bone mass in the early stage of the disease and the possibility to influence it by calcium and vitamin D

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Ceska Revmatologie (Czech Republic), 1998, 6/2 (39-47)

The authors present a report on an investigation implemented in the framework of a grant. The objective was to investigate patients with rheumatoid arthritis in the early stage of the disease and assess the rate of loss of bone mass and the possibility to influence it by the most frequently used and most economical treatment with calcium and vitamin D. Already in the early stage of the disease after a maximum of three years the mean bone density (BMD) is by 0.5 to 0.9 units of the T-score below the mean in healthy people or even much lower. During a two-year follow upod in all patients (with a negligible exception) a further significant drop of the BMD was recorded, on average by 5%, i.e. 2.5% per year. This rate of loss of bone mass is important from the aspect of premature development of osteoporosis . Examination of markers of bone turnover revealed an increased osteoresorption without increased new formation. On average it was small, but in some cases it was marked. Calcium therapy (1000 mg/day and vitamin D 8000 u./day) suppressed signs of enhanced osteoresorption, but did not affect the loss of bone mass. The trial proceeds now beyond the framework of the grant in order to assemble data over a longer period of time and confront them with some parameters of the basic disease.

The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density

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Journal of Bone and Mineral Research (USA), 1997, 12/7 (1049-1057)

Previous studies of the vitamin D receptor (VDR) polymorphisms and bone mineral density (BMD) have suggested that there may be differences in calcium absorption among groups of women with different VDR genotypes, and that the association may be stronger in younger women. To investigate the association between the VDR polymorphisms and BMD, this study was undertaken in the Framingham Study Cohort and a group of younger volunteers. Subjects from the Framingham Study (ages 69-90 years) included those who underwent BMD testing and who had genotyping for the VDR alleles (n = 328) using polymerase chain reaction methods and restriction fragment length polymorphisms with BsmI (B absence, b presence of cut site). A group of younger volunteer subjects (ages 18-68) also underwent BMD testing and VDR genotyping (n = 94). In Framingham Cohort subjects with the bb genotype, but not the Bb or BB genotypes, there were significant associations between calcium intake and BMD at five of six skeletal sites, such that BMD was 7-12% higher in those with dietary calcium intakes greater than 800 mg/day compared with those with intakes <500 mg/day. The data also suggested that BMD was higher in persons with the bb genotype only in the group with calcium intakes above 800 mg/day. No significant differences were found in the Framingham Cohort for age-, sex-, and weight-adjusted BMD at any skeletal site between those with the BB genotype and those with the bb genotype regardless of 25-hydroxyvitamin D levels or country of origin. In the younger volunteers, BMD of the femoral neck was 5.4% higher ($p < 0.05$) in the bb genotype group compared with the BB group and 11% higher ($p < 0.05$) in males with the bb genotype compared with the BB group. There were no significant differences at the lumbar spine. In this study, the association between calcium intake and BMD appeared to be dependent upon VDR genotype. The finding of an association between dietary calcium intake and BMD only in the bb genotype group suggests that the VDR genotype may play a role in the absorption of dietary calcium. Studies that do not consider calcium intake may not detect associations between VDR genotype and BMD. In addition, the association between VDR alleles and BMD may become less evident in older subjects.

The effect of 1,25(OH)2 vitamin D3 on CD4+/CD8+ subsets of T lymphocytes in postmenopausal women

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Life Sciences (USA), 1997, 61/2 (147-152)

The effect of exogenous 1,25(OH)2 vitamin D3 (1,25(OH)2D3) on the CD3+, CD4+ and CD8+ subsets (counts/ul) of T lymphocytes was investigated in two randomized groups of post menopausal women. Group one (16 subjects) received 1ug/day of the secosteroid for 14 days, while group two (14 participants) was treated with 2 ug/day for the same period. The placebo group comprised another 10 postmenopausal women. Compliance of the treatment was controlled by serum intact parathyroid hormone (PTH) levels, which markedly declined at the end of

the treatment ($p<0.01$ for both doses). The vitamin D status of the women before the treatment was defined by serum 25(OH) vitamin D (25(OH)D) levels. The lower dose of the secosteroid did not change any of the measured immune parameters. After a higher dose of 1,25(OH)2 D3 the mean values of CD3+ and CD8+ increased ($p<0.05$ for the both parameters), but no changes in total lymphocytes and the CD4+ subset were observed. There were no correlations between the immune response DeltaCD3+, DeltaCD4+ and DeltaCD8+) and basal circulating 25(OH)D. Briefly, then, 1,25(OH)2D3 slighly but significantly increases CD3+ and CD8+ subsets independently on the initial vitamin D status of the postmenopausal women.

Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of five currently available calcium salts in healthy male volunteers

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Several calcium supplements are currently available and many of them are marketed without proper comparison of the bioavailability of the actual preparations. The aim of the present trial was to evaluate and compare the acute changes in serum calcium (Ca) and parathyroid hormone (PTH) levels following the oral administration of a vehicle and of five calcium salts currently prescribed in Western Europe. No significant changes in serum Ca or PTH levels were observed after administration of the vehicle. All calcium salts induced significant increases in serum Ca and decreases in serum PTH compared to baseline values. Comparison of the six response curves revealed a significantly greater increase in serum Ca and a greater decrease in serum PTH after each of the calcium salts than observed after the vehicle. However, no statistically significant differences were observed between the different calcium salts for serum Ca increments. The decrease in serum PTH observed after administration of an ossein-hydroxyapatite complex was significantly less important than after the four other calcium salts, even if statistically different than after vehicle. When assessing the area under the curve (AUC) of PTH values, we observed that calcium carbonate and citrate induce a significantly greater decrease in serum PTH than the other calcium salts which are, however, statistically more active than the vehicle. Serum PTH is decreased under the lower limit of the normal range (10 pg/ml), between t60 and t120 for calcium carbonate and citrate and between t60 and t90 for calcium gluconolactate while the mean PTH values remain within the normal range throughout the study with calcium pidolate, the ossein-hydroxyapatite complex and the vehicle. In conclusion, all calcium preparations significantly increase serum calcium and decrease serum parathormone, ompared to what is observed after oral intake of a vehicle. However, significant differences in suppression of

parathormone are observed between the different calcium preparations and might h of importance for their clinical use.

1-alpha-hydroxyvitamin D3 treatment decreases bone turnover and modulates calcium-regulating hormones in early postmenopausal women

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Bone (USA), 1997, 20/6 (557-562)

50 Japanese women within 10 years after menopause (mean age 52.5 years) were studied to determine the effects of 0.75 microg of 1-alpha-hydroxyvitamin D3 (1-alpha-(OH)D3) with calcium (150 mg/day) (treated group: N = 25) and calcium only (control group: N = 25) for 12 months on bone mass and metabolism. Their L2-4 BMD measurements were 1.5 SD below the mean value of Japanese young, normal women, L2-4 BMDs increased significantly in the treated group (+2.1%; $p < 0.01$), but decreased significantly in controls (-2.l%; $p < 0.01$). Although serum calcium and creatinine remained unchanged in both groups, phosphorus levels increased significantly in the treated group ($p < 0.01$). Urinary calcium/creatinine (Cr) increased in both groups. Urinary pyridinoline/Cr and deoxypyridinoline/Cr decreased significantly in the treated group ($p < 0.05$), but not in the control group. Serum osteocalcin levels remained unchanged in both groups, Intact parathyroid hormone levels decreased significantly ($p < 0.05$) and calcitonin levels significantly increased in the treated group ($p < 0.05$), but these changes were not observed in the control group. These data clearly demonstrate that 0.75 microg of 1-alpha-(OH)D3 maintained bone mass by reducing bone resorption by modulation of calcium-regulating hormones. Temporarily increased urinary calcium excretion was observed in control group, but did not appear to be effective in modulating bone turnover.

Role of dietary lipid and antioxidants in bone metabolism

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Nutrition Research (USA), 1997, 17/7 (1209-1228)

Recent investigations and clinical studies suggest that dietary lipids and antioxidant nutrients influence bone formation and cartilage biology. In animals, bone modeling appears to be optimal when (n-3) fatty acids are supplied in thediet to moderate the metabolic and physiologic effects of (n- 6) fatty acids. In osteoporosis, greater osteoclastic activity results in excessive mineral loss and bone destruction. New evidence supports the idea that dietary fatty acids and

antioxidants can attenuate osteoclastic activity to reduce the severity of osteolytic diseases of the bone and joint. Moreover,(n-6) fatty acids may aggravate the deficiency of antioxidant enzyme protective systems in epiphyseal cartilage of long bones. For example, vitamin E was reported to increase in vivo trabecular bone formation rate and to restore collagen synthesis in chondrocytes enriched with linoleic acid. This review presents new information that documents a role for dietary lipids and antioxidants in supporting bone formation and cartilage function for optimal health.

The response to calcitriol therapy in postmenopausal osteoporotic women is a function of initial calcium absorptive status

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Calcitriol is used in the treatment of osteoporosis but the indications for its use have not been clearly defined. Because it stimulates calcium absorption, we have tended to select osteoporotic patients with low calcium absorption for this therapy and now report the results. We measured the hourly fractional rate of calcium absorption (alpha) with 45Ca and fasting urinary calcium /creatinine (Ca/Cr) and hydroxyproline/creatinine (OHPr/Cr) in 103 postmenopausal women aged 68 (0.67SE) years with vertebral compression fractures (77) or forearm or vertebral bone density below the young normal range (26). They were given 0.25 microg daily of calcitriol (Rocaltrol, Roche, Basle, Switzerland) with a 1g calcium supplement daily for 6-12 weeks, when the biochemical tests were repeated. Initial OHPr/Cr was inversely related to initial alpha (P=0.001) and positively to initial Ca/Cr (P<0.001). alpha rose on therapy from 0.47 (0.018) to 0.59 (0.018) per hour (P<0.001) and OHPr/Cr fell in the whole group from 19.1 (0.83) to13.8 (0.58) (P< 0.001). The change in alpha on therapy (corrected for the 'regression to the mean effect') was inversely related to initial alpha (P<0.001) as was the change in OHPr/Cr (P=0.001). There was no relationship, however, between initial Ca/Cr and either the rise in alpha or the fall in OHPr/Cr on therapy. The data support the concept that low calcium absorption is a cause of negative calcium balance in postmenopausal osteoporosis and that the effectiveness of calcitriol therapy is inversely related to the initial rate of calcium absorption.

Postprandial parathyroid hormone response to four calcium-rich foodstuffs

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We studied the effects of four calcium-rich foodstuffs on postprandial parathyroid hormone secretion. Four hundred milligrams calcium from either Emmental cheese, milk, sesame seeds, spinach, or calcium salt (calcium lactate gluconate + calcium carbonate) or no additional calcium (control session) were given to nine female volunteers immediately after a first blood sample (at 0900) in random order with a light standardized meal containing 37 mg Ca. Blood samples were taken at 0900 (before the calcium load), 1000, 1100, 1300, and 1500 at every study session. Urine was collected during the sessions. Serum ionized calcium, phosphate, magnesium, intact parathyroid hormone, and urinary calcium excretion were measured. The serum ionized calcium concentration increased significantly after ingesting cheese (P=0.004, contrast analysis) or calcium salt (P=0.05, contrast analysis) compared with the control session. Compared with the control session, the serum phosphate concentration increased after the cheese session (P=0.004, contrast analysis) and after the milk session (P=0.02, contrast analysis). Calcium salt (P=0.007, contrast analysis) and cheese (P=0.002, contrast analysis) caused a significant decline in serum intact parathyroid hormone compared with the control session. The urinary calcium excretion with cheese was 141% (P=0.001), with milk was 107% (P=0.004), and with calcium salt was 75% (P= 0.02) above that of the control session. Our results show that calcium from sesame seeds and spinach does not cause an acute response in calcium metabolism. Our results indicate that fermented cheese could be a better dietary source of calcium than milk when the metabolic effects of the foodstuffs are considered.

Complementary medical treatment for Colles' fracture: A comparative, randomized, longitudinal study

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Calcified Tissue International (USA), 1997, 60/6 (567-570)

In 45 women with Colles' fracture, two types of complementary medical treatment (calcitonin with calcium (SCT+Ca) and calcium alone (Ca)) were compared with placebo. Consecutive patients were assigned randomly to one of the three study groups at the time of inclusion in the study: 15 women (68.6 +/- 5.7 years) were given 100IU/day IM of SCT plus 1200 mg of elemental Ca for 10 successive days each month; 15 women (71.7 +/- 6.1 years) were given only 1200 mg of elemental Ca for 10 days each month; and 15 women (66.9 +/-7.9 years) were treated with placebo. Biochemical and radiogrammetric studies were made at baseline and after 1 year of treatment. In the SCT+Ca group tartrate-resistant acid phosphatase decreased (Wilcoxon test, P =0.014) and the metacarpal index and the cortical and total area (CA/TA) ratio increased (both P =0.001). In the group treated with Ca alone, no changes were observed. In the placebo group, the metacarpal index and CA/TA decreased (P = 0.015 and P = 0.007, respectively). Ca alone, at the dosage used here, inhibited bone loss after Colles' fracture. The addition of SCT to Ca

administration not only impeded bone loss but significantly increased cortical bone mass.

Calcium and vitamin D in the prevention and treatment of osteoporosis

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Journal of Clinical Rheumatology (USA), 1997, 3/2 Suppl. (S52-S56)

An increasing prevalence of calcium and/or vitamin Ddeficiency in the general population (especially, but not only, in elderly subjects) has been emphasized in recent epidemiologic studies. These deficiencies could be responsible for accelerated bone loss mediated by secondary hyperparathyroidism and increased bone turnover and could explain the dramatic increase of the incidence of osteoporotic fractures with age. High calcium intake in prepubertal girls seems to be associated with higher peak bone mass in late adolescence. Calcium supplementation could slow bone turnover and bone loss in particular subsets of patients, including calcium- deficient postmenopausal women and elderly patients. A specific antifracture effect of calcium supplementation in postmenopausal osteoporotic patients has not been established, but a calcium-plus-low-dose-vitamin D3 supplementation has been suggested to decrease the peripheral fracture incidence (especially hip fracture) in elderly institutionalized women. After a critical review of these data, some practical recommendations are suggested.

Calcium intake and fracture risk: Results from the study of osteoporotic fractures

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American Journal of Epidemiology (USA), 1997, 145/10 (926-934)

The relation between dietary calcium, calcium, and vitamin D supplements and the risk of fractures of the hip (n = 332), ankle (n = 210), proximal humerus (n = 241), wrist (n = 467), and vertebrae (n = 389) was investigated in a cohort study involving 9,704 US white women aged 65 years or older. Baseline assessments took place in 1986-1988 in four US metropolitan areas. Dietary calcium intake was assessed at baseline with a validated food frequency questionnaire. Data on new nonvertebral fractures were collected every 4 months during a mean of 6.6

years of follow-up; identification of new vertebral fractures was based on comparison of baseline and follow-up radiographs of the spine done a mean of 3.7 years apart. Results were adjusted for numerous potential confounders, including weight, physical activity, estrogen use, protein intake, and history of falls, osteoporosis, and fractures. There were no important associations between dietary calcium intake and the risk of any of the fractures studied. Current use of calcium supplements was associated with increased risk of hip (relative risk = 1.5, 95% confidence interval 1.1-2.0) and vertebral (relative risk = 1.4, 95% confidence interval 1.1-1.9) fractures; current use of Tums antacid tablets was associated with increased risk of fractures of the proximal humerus (relative risk = 1.7, 95% confidence interval 1.3-2.4). There was no evidence of a protective effect of vitamin D supplements. Although a true adverse effect of calcium supplements on fracture risk cannot be ruled out, it is more likely that our findings are due to inadequately controlled confounding by indications for use of supplements. In conclusion, this study did not find a substantial beneficial effect of calcium on fracture risk.

Effect of dietary calcium on urinary oxalate excretion after oxalate loads

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American Journal of Clinical Nutrition (USA), 1997, 65/5 (1453-1459)

An experimental model that allowed differentiation between endogenously and exogenously derived urinary oxalate was used to assess the effect of different forms and doses of ingested calcium on oxalate absorption and excretion. In replication 1 (R-1), subjects participated in three oxalate load (OL) tests: baseline (OL alone), calcium carbonate (OL with concomitant calcium carbonate ingestion), and calcium citrate malate (CCM) (OL with concomitant CCM ingestion). The calcium salts each provided 300 mg elemental Ca. OLs consisted of 180 mg unlabeled and 18 mg 1,2(13C2)oxalic acid. In R-2, subjects participated in four OL tests: baseline (OL alone) and OLs administered concomitantly with 100, 200, or 300 mg Ca. Timed urine samples after the OL were collected at 2-h intervals for the initial 6 h and samples were pooled into 9-h aliquots for the remaining 18 h of the 24 h period. In R-1, 24-h mean exogenous oxalate decreased ($P < 0.05$) after the OL from 36.2 mg (baseline) to 16.1 mg (after calcium carbonate) and to 14.3 mg (after CCM) whereas endogenous oxalate remained relatively constant. Mean 24-h oxalate absorption decreased significantly from that at the time of the baseline treatment (18.3%) after both calcium carbonate (8.1%) and CCM (7.2%) treatments. In R-2, mean 24-h oxalate absorption was significantly lower after 200 (5.9%) and 300 (7.6%) mg Ca than after 100 mg Ca (9.1%) and the OL alone (11.3%). Concomitant meal ingestion significantly decreased oxalate absorption in the absence of dietary calcium but not in association with the 300-mg Ca treatment. The overall data provide definitive evidence that dietary calcium can reduce oxalate absorption and excretion. Calcium carbonate and CCM were equally effective in this regard and a

minimum of 200 mg elemental Ca maximized this effect in conjunction with an oxalic acid intake of 198 mg.

1alpha-Hydroxyvitamin D2 partially dissociates between preservation of cancellous bone mass and effects on calcium homeostasis in ovariectomized rats

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Calcified Tissue International (USA), 1997, 60/5 (449-456)

Vitamin D metabolites can prevent estrogen depletion-induced bone loss in ovariectomized (OVX) rats. Our aim was to compare the bone-protective effects of 1alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3), 1alpha,25-dihydroxyvitamin D2 (1,25(OH)2D2), 1alpha-hydroxyvitamin D3 (1alpha(OH)D3), and 1alpha-hydroxyvitamin D2 (1alpha(OH)D2) in OVX rats.1alpha(OH)D3 and 1alpha(OH)D2 are thought to be activated in the liver toform 1,25(OH)2D3 and 1,25(OH) 2D2, respectively. Forty-four 12-week-old female Fischer-344 rats were either OVX or sham- operated (SHAM). Groups of OVX rats (n = 7 each) received vehicle alone, 1,25(OH)2D3, 1,25(OH)2D2, 1alpha(OH)D3, or 1alpha(OH)D2, starting 2 weeks after surgery. All vitamin D metabolites were administered orally at a dose of 15 ng/day/rat. Urine and blood samples were collected 6, 9, 12, and 16 weeks after surgery. Serum samples were analyzed for total calcium and phosphate. Calcium, phosphate, creatinine, and free collagen cross-links (ELISA) were determined in urine. After tetracycline double labeling, the rats were sacrificed 16 weeks postsurgery, and the proximal tibiae and the first lumbar vertebrae were processed undecalcified for static and dynamic bone histomorphometry.1,25(OH)2D3 and, to a slightly lesser extent, 1,25 (OH) 2D2 elevated vertebral cancellous bone mass in OVX rats to a level beyond that observed in SHAM animals, and both compounds increased serum calcium and urinary calcium excretion to similar extents. 1alpha(OH)D3 and 1alpha(OH)D2 resulted in a 64% and 84%, respectively, inhibition of ovariectomy-induced vertebral cancellous bone loss. In the proximal tibial metaphysis, all vitamin D metabolites tested could only partially prevent post-OVX trabecular bone loss, with a tendency for 1alpha(OH)D3 to be the least active compound. The effects of 1alpha(OH)D3 and 1alpha(OH)D2 on calcium homeostasis differed markedly, however. The mean increase in urinary calcium excretion over the whole experiment was fivefold for 1alpha(OH)D3, whereas the corresponding increase for 1lpha(OH)D2 was only twofold. We conclude that, compared with 1alpha(OH)D3, 1alpha(OH)D2 combined at least equal or higher bone-protective activity in OVX rats with distinctly less pronounced effects on calcium homeostasis. This effect was not due to a differential action of the corresponding main activation products, 1,25(OH)2D3 and 1,25(OH)2D2.

A high dietary calcium intake is needed for a positive effect on bone density in Swedish postmenopausal women

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Osteoporosis International (United Kingdom), 1997, 7/2 (155-161)

The importance of dietary calcium for bone health is unclear, partly since most investigations have dealt only with a fairly narrow range of calcium intake. In the present population-based observational study with longitudinal dietary assessment, we investigated women with a mean age of 60 years and with a consistently high (range 1417-2417, mean 1645 mg, n = 40), intermediate (80-1200, mean 1006 mg, n = 35) or low (400-550, mean 465 mg, n = 40) estimated daily consumption of calcium. Measurements of bone mineral density (BMD) of the lumbar spine, femoral neck and total body were performed by dual-energy X-ray absorptiometry, as well as ultrasound of the heel. In a multivariate analysis, with adjustment for energy intake the risk factors for osteoporosis (age, body mass index, physical activity, menopausal age, use of estrogens, smoking and former athletic activity), the group with the highest calcium intake had higher values for BMD than the others at all measured sites. The average mean difference compared with the low and the intermediate calcium group was 11% for the femoral neck, 8-11% for the lumbar spine and 5-6% for total body BMDs. In univariate analyses and multivariate models which did not include energy intake, the differences between the groups were less pronounced. The women in the intermediate calcium group had approximately the same mean BMD values as those in the low calcium group. These findings support the view that only a high calcium intake (3% highest percentiles in the studied population) protects against osteoporosis in Swedish postmenopausal women.

Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1alpha-hydroxyvitamin D3 and calcium supplementation

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Stroke (USA), 1997, 28/4 (736-739)

Background and Purpose: It has been demonstrated that bone mass was significantly reduced on the hemiplegic side of stroke patients, which might increase their risk of hip fracture. We evaluated the efficacy of 1alpha-hydroxyvitamin D3 (1alpha(OH)D3) and supplemental elemental calcium in maintaining bone mass and decreasing the incidence of hip fractures after hemiplegic stroke.

Methods: In a randomized study, 64 patients with hemiplegia after stroke with a mean duration of illness of 4.8 years received either 1 microg 1alpha(OH)D3 daily (treatment group, n=30) or an inactive placebo (placebo group, n=34) for 6 months and were observed for this duration. Both groups received 300 mg of

elemental calcium daily. The bone mineral density (BMD) and metacarpal index (MCI) in the second metacarpals were determined by computed x-ray densitometry. The incidence of hip fractures in these patients was recorded.

Results: BMD on the hemiplegic side decreased by 2.4% in the treatment group and 8.9% in the placebo group (P=.0021), while BMD on the intact side increased by 3.5% and decreased by 6.3% in the treated and placebo groups, respectively (P=.0177). In the treatment group, the difference in BMD between hemiplegic and nonhemiplegic sides decreased significantly compared with that before randomization. This difference increased in the placebo group. We observed a similar improvement in MCI in the treatment group but not in the placebo group. Four patients in the placebo group suffered a hip fracture compared with none in the treatment group (P=.0362).

Conclusions: Treatment with 1alpha(OH)D3 and supplemental elemental calcium can reduce the risk of hip fractures and can prevent further decreases in BMD and MCI on the hemiplegic side of patients with a long-standing stroke. Treatment also may improve these indices on the intact side.

Effects of growth hormone (GH) replacement on bone metabolism and mineral density in adult onset of GH deficiency: Results of a double-blind placebo-controlled study with open follow-up

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European Journal of Endocrinology (Norway), 1997, 136/3 (282-289)

It's known that GH stimulates bone turnover and GH-deficient adults have a lower bone mass than healthy controls. In order to evaluate the influences of GH replacement therapy on markers of bone turnover and on bone mineral density (BMD) in patients with adult onset GH deficiency, a double-blind placebo-controlled study of treatment with recombinant human GH (rhGH; mean dose 2.4IU daily) in 20 patients for 6 months and an extended open study of 6 to12 months were conducted. Eighteen patients, fourteen men and four women, with a mean age of 44 years with adult onset GH deficiency were evaluated in the study. Compared with placebo, after 6 months serum calcium (2.39 + or - 0.02 vs 2.32 +or- 0.02 mmol/l, P=0.037) and phosphate (0.97 + or -0.06 vs 0.75 + or - 0.05 mmol/l, P=0.011) increased and the index of phosphate excretion (0.03 +or - 0.03 vs 0.19 + or - 0.02, P<0.001) decreased significantly, and there was a significant increase in the markers of bone formation (osteocalcin, 64.8 + or -11.8 vs 17.4 +or -1.8 ng/ml, P<0.001; procollagen type I carboxyterminal propeptide (PICP), 195.3 plus or minus 26.4 vs 124.0 + or - 15.5 ng/ml, P=0.026) as well as those of bone resorption (type I collagen carboxyterminal telopeptide (ICTP), 8.9 plus or minus 1.2 vs 3.3 + or - 0.5 ng/ml, P<0.001; urinary hydroxyproline, 0.035 + or - 0.006 vs 0.018 + or - 0.002 mg/100 ml glomerular filtration rate, P=0.009). BMD did not change during this period of time. IGF-I was significantly higher in treated patients (306.5 + or - 45.3 vs 88.7 + or - 22.5 ng/ml, P<0.001). An analysis of the

data compiled from 18 patients treated with rhGH for12 months revealed similar significant increases in serum calcium and phosphate, and the markers of bone turnover (osteocalcin, PICP, ICTP, urinary hydroxyproline). Dual energy x-ray absorptiometry (DXA)-measured BMD in the lumbar spine (1.194 + or - 0.058 vs 1.133 + or - 0.046 g/cm2, P=0.015), femoral neck (1.009 plus or minus 0.051 vs 0.936 + or - 0.034 g/cm2, P=0.004), Ward=s triangle (0.881 + or - 0.055 vs 0.816 + or - 0.04 g/cm2, P=0.019) and the trochanteric region (0.869 + or - 0.046 vs 0.801 + or - 0.033 g/cm2, P=0.005) increased significantly linearly (compared with the individual baseline values). At 12 months, BMD in patients with low bone mass (T-score < -1.0 S.D.) increased more than in those with normal bone mass (lumbar spine 11.5 vs 2.1%, P=0.030, and femoral neck 9.7 vs 4.2%, P= 0.055). IGF-I increased significantly in all treated patients. In conclusion, treatment of GH-deficient adults with rhGH increases bone turnover for at least 12 months, BMD in the lumbar spine and the proximal femur increases continuously in this time (open study) and the benefit is greater in patients with low bone mass. Therefore, GH-deficient patients exhibiting osteopenia or osteoporosis should be considered candidates for GH supplementation. However, long-term studies are needed to establish that the positive effects on BMD are persistent and are associated with a reduction in fracture risk.

Decreased serum IGF-I and dehydroepiandrosterone sulphate may be risk factors for the development of reduced bone mass in postmenopausal women with endogenous subclinical hyperthyroidism

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European Journal of Endocrinology (Norway), 1997, 136/3 (277-281)

Postmenopausal women with endogenous subclinical hyperthyroidism seem to have reduced bone mass, which does not correlate with serum thyroid hormone levels. Relative insufficiencies of IGF-I and dehydroepiandrosterone sulphate (DHEAS) might be additional risk factors for low bone density in these patients. We measured IGF-I, IGF-binding protein-3 (IGFBP-3) and DHEAS levels together with bone mineral density (BMD) of the femoral neck and lumbar spine in women with an autonomously functioning thyroid nodule. Sixty-three women were classified as subclinical hyperthyroid (31 pre- and 32 postmenopausal) and 39 as overt hyperthyroid (16 pre- and 23 postmenopausal) and results were compared with data obtained from 41age- matched euthyroid healthy women. In premenopausal women BMD was reduced only in the overt hyperthyroid group, and only in the spine, to 92% (P < 0.05). Serum IGF-I as well as IGFBP-3 were increased in the manifest hyperthyroid group, to 157% (P < 0.001) and 129% (P < 0.05) respectively, whereas DHEAS levels did not change in either premenopausal patient group. In postmenopausal women BMD was significantly reduced both in the subclinical hyperthyroid group (spine to 90% and femoral neck to 88%; P < 0.05), as well as in the hyperthyroid group (spine to 78% and femoral neck to 86%; P < 0.01). In contrast to premenopausal women, serum IGF-I and IGFBP-3 did not change in the two groups who were postmenopausal and

serum DHEAS levels were reduced to 58% ($P < 0.001$) in both postmenopausal groups with subclinical as well as overt hyperthyroidism. In the same two groups of patients, serum IGF-I and DHEAS levels correlated with BMD (femoral neck; both $r = 0.50$, $P < 0.05$). In conclusion, women with a solitary autonomous thyroid nodule with subclinical hyperthyroidism have reduced BMD only if they are postmenopausal. This is probably due to the effect of subtle increases in thyroid hormone production together with lack of oestrogen protection of the skeleton. But additional risk factors for the development of enhancd bone loss might be a state of relative IGF-I and DHEAS insufficiency in these patients as well as in postmenopausal women with overt hyperthyroidism.

Osteoporosis: Prevention, diagnosis, and management

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American Journal of Medicine (USA), 1997, 102/1 A (35S-39S)

Osteoporosis is a public health scourge that is usually eminently preventable. Some risk factors, such as low calcium intake, vitamin D deficiency, and physical inactivity, are amenable to early interventions that will help maximize peak bone density. Other risk factors subject to modification are cigarette smoking and excessive consumption of protein, caffeine, and alcohol. Hip fractures are the most serious outcome of osteoporosis, with enormous personal and public health consequences. The ongoing Study of Osteoporotic Fractures has identified additional independent predictors of hip fracture risk, including maternal hip fracture, absence of significant weight gain since age 25, height, hyperthyroldism, use of long- acting benzodiazepines or anticonvulsants, spending <4 hours a day on one's feet, inability to rise from a chair without using one's arms, poor visual depth perception and contrast sensitivity, and tachycardia. In an individual perimenopausal woman, the risk of osteoporotic fracture and the urgency of estrogen replacement therapy can be best estimated on the basis of bone mineral density, as measured by dual-energy x-ray absorptiometry, coupled with the presence or absence of existing fractures and clinical risk factors evident from the history and physical examination. Estrogen, calcitonin, and bisphosphonates have all been proved effective in retarding postmenopausal bone loss and therefore reducing the risk of fracture. The use of sodium fluoride is more controversial, although a recent study has suggested a possible role for slow-release fluoride combined with high-dose calcium supplementation.

Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes

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Vitamin D deficiency, which causes osteomalacia, may also be important in the pathogenesis of age-related osteoporosis. We studied serum vitamin D metabolites in 52 young women (mean age: 30 + or - 3 y; range: 25-35y), 64 elderly free-living women (mean age: 71 + or - 4 y; range: 65-82 y) and 60 elderly women living in nursing homes (mean age: 84 plus or minus 9 y; range: 61-102 y). Mean serum 25-hydroxyvitamin D (calcidiol) was 10.8 plus or minus 4.4 nmol/L (27 + or - 11 ng/mL) in women living in nursing homes and was similar to that of free- living young (11.3 plus or minus 4.2 nmol/L, or 28 + or - 10 ng/mL) and elderly (11.5 plus or minus 3.2 nmol/L, or 29 plus or minus 8 ng/mL) women. Vitamin D deficiency (defined as serum calcidiol < 4.8 nmol/L, or 12 ng/mL) occurred in 8% of women living in nursing homes, in 6% of the young women, and in 1.6% of the free-living elderly women. Serum calcidiol was significantly correlated with vitamin D intake ($r = 0.25$, $P < 0.05$) and inversely correlated with serum intact parathyroid hormone (iPTH) ($r = -0.16$, $P < 0.03$). Serum iPTH increased with age and secondary hyperparathyroidism was observed in 17% of the women living in nursing homes. Calcium absorption declined with age, but calcium absorption and serum 1alpha,25-dihydroxyvitamin D (calcitriol) were significantly lower in women living in nursing homes, which probably contributed to the secondary hyperparathyroidism. In conclusion, normal serum calcidiol may avoid the problem of osteomalacia, but it does not correct malabsorption of calcium. Although calcitriol corrects the malabsorption of calcium, it remains to be seen whether higher amounts of vitamin D can normalize the calcium malabsorption of aging.

Effect of 1,25(OH)2 vitamin D3 on circulating insulin-like growth factor-I and beta2 microglobulin in patients with osteoporosis

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Calcified Tissue International (USA), 1997, 60/3 (236-239)

To test the hypothesis that growth factors mediate the stimulatory effect of 1,25(OH)2 vitamin D3 (1,25(OH)2D3) on bone remodeling in osteoporosis, the authors studied the effect of the secosteroid administration in two closes (1 microg and day and 2 microg/day) for 14 days on circulating insulin-like growth factor-I (IGF-I), beta2 microglobulin, anti osteocalcin in 18 osteoporotic women. The biological effectiveness of the treatment was controlled by a decline of serum intact parathyroid hormone. Compared with the values before treatment, 1,25(OH)2D3 increased means of plasma IGF I, beta2 microglobulin, and serum osteocalcin significantly: however, the effects were only apparent after the higher dose of the drug (169 + or - 26 versus 134 + or - 28 ng/ml, $P < 0.01$; 2.08 + or - 0.1 versus 1.92 plus or minus 0.1 microg/ml, $P < 0.05$; and 8.5 plus or minus 1.3 versus 5.4 + or - 1.1 ng/ml, $P < 0.01$, respectively). The authors conclude that exogenous 1,25(OH)2D3 promotes the production of IGF-I and beta2 microglobulin in osteoporotic patients in parallel to the marker of osteoblastic function, osteocalcin, which supports the tested hypothesis.

Influence of the vitamin D receptor gene alleles on bone mineral density in postmenopausal and osteoporotic women

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Journal of Bone and Mineral Research (USA), 1997, 12/2 (241-247)

It's well established that genetic factors contribute to bone turnover and bone density. Evidence exists suggesting that a major part of this genetic influence may be due to polymorphisms in the vitamin D receptor (VDR) gene. However, it=s not clear whether the VDR genotype effect persists in elderly women. In the present study, the relationship between the BsmI, ApaI, and TaqI polymorphisms in the VDR gene, and the bone mineral density (BMD) at the lumbar spine, the femoral neck (FN), and the proximal radius was investigated in a large group of elderly women (75.5 plus or minus 5.0 years) of Caucasian origin and in 84 Type I osteoporotic women (66.6 + or - 8.4 years). We did not find a correlation between the VDR genotypes and BMD in elderly women. However, a significantly higher FN-BMD was observed in obese (body mass index (BMI) > 30 kg/m2) versus nonobese (BMI < 30 kg/m2) women ($p < 0.01$). This relationship was observed for all BsmI genotypes. Furthermore, the FN-BMD of nonobese women with bb BsmI genotype was 5% higher than that of women with the BB genotype ($p = 0.04$). We conclude that the VDR gene polymorphisms influence the FN-BMD in nonobese postmenopausal women. In a second part of the study, possible correlations between the VDR gene polymorphisms and osteoporosis Type I were analyzed. Our data could not reveal any association between these parameters.

Connections between phospho-calcium metabolism and bone turnover. Epidemiologic study on osteoporosis (second part)

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Minerva Medica (Italy), 1996, 87/12 (565-576)

Background. The recent development of highly accurate and precise osseous mass quantitative evaluation methodology, permits the conduction, in the sphere of osteoporosis, of epidemiologic investigations no longer limited solely to fracture complications, but also based on the definition of osseous mass. Fractures being only complications, possible but not certain, of the advanced stages of the disease, the studies based on their incidence allow one to underestimate the global entity of prevalence and incidence, besides building only a partially useful reference in view of primary and secondary prevention.

Methods. The main points of our study are the following:

1) Evaluation of the incidence of the primary risk factors for osteoporosis as they appear in the literature, on the bone mass values of examined subjects, utilizing static mineralometric data as a reference standard;

2) Study of biohumoral data relative to phospho-calcium metabolism and to sexual function, to show the possibility of their use as early identifying markers of subjects at risk; reference values represented by dynamic mineralometric data. The principal conclusions that emerged in the course of the study are the following.

Results.In relation to the use of phospho-calcium metabolic biohumoral and hormonal variables, as a predictive function on the variations of bone turnover, the variables:osteocalcin, alkaline phosphatase, alkaline phos-phatase bone isoenzyme, hydroxyprolinuria/creatininuria, have resulted significantly different in the comparison between high and low turnover subjects. The degree of quantitative correlation of such variables with the entity of percentage decrement of bone mass has been modest. The overall value of R-square of the predictive model, besides the variables mentioned the value of bone mass at 1degreecontrol visit, was 0.38(osteocalcin:0 .27; osteocalcin+hydroxyprolinuria /creatininuria: 0.33; preceding variables + bone mass at 1st control: 0.36; preceding variables + alkaline phosph-atase:0.37; preceding variables +alkaline phosphatase bone isoenzyme:0.38).

Conclusions.The single value osteocalcin may furnish indications on the future variations of bone turnover and consequently on the early identification of the subjects at risk for osteoporosis at high turnover; the addition of the other variables indicated in our predictive model allows an increase of the possibilities of individualizing of these subjects.

Treatment of post-menopausal osteoporosis with recombinant human growth hormone and salmon calcitonin: A placebo controlled study

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Clinical Endocrinology (United Kingdom), 1997, 46/1 (55-61)

Objective: The usefulness of GH in the treatment of post-menopausal osteoporosis (PMO) is still debated. We have studied the effects of recombinant human GH (rhGH) given alone or in combination with salmon calcitonin (sCT)in the treatment of PMO.

Patients: Thirty women with established PMO (aged 61.1 + or - 4.4 years) were divided into 3 groups of 10 and randomly assigned to 3 treatment sequences: rhGH (12 IU/day) s.c. for 7 days, followed by sCT (50 IU/day) s.c. for 21 days and by 61 days without treatment (group 1); placebo for 7 days, followed by sCT for 21 days and by 61 days without treatment (group 2); rhGH for 7 days,

followed by placebo for 21 days, and by 61 days without treatment (group 3). Each cycle was repeated 8 times (24 months).

Measurements: At days 0, 8, 29 and 90 of each cycle, serum IGF-I, calcium, phosphate, osteocalcin, alkaline phosphatase and urinary excretion of calcium, hydroxyproline and pyridinoline cross-links (Pyr) were measured. At months 0, 6, 12, 18 and 24, bone mineral density (BMD) was measured by dual-photon absorptiometry (DPA), at lumbar spine (LS), femoral shaft (F) and distal radius (DR).

Results: A significant increase in serum osteocalcin and urinary calcium, hydroxyproline and Pyr was detected after each rhGH period. In group 1, BMD at lumbar spine increased by 2.5% at year 2; in contrast, significant ($p < 0.05$) decreases in BMD-LS values were found in patients treated with CT and placebo (group 2) and with OH and placebo (group 3). BMD-F did not show any significant change in patients of group 2, but a significant ($p < 0.05$) decrease was found in groups 1 and 3. BMD-DR did not show any significant change with respect to baseline in any of the three groups. No significant difference between the three groups was found in bone mass at the three different regions.

Conclusions: Our study demonstrates that treatment with rhGH increases bone turnover in postmenopausal osteoporotic women. Combined treatment with rhGH and CT over a period of 24 months is able to maintain bone mass at lumbar spine and distal radius, but induces a decline at femoral shaft; therefore, it does not seem particularly useful in the therapy of post-menopausal osteoporosis. :

Effect of measuring bone mineral density on calcium intake

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Japanese Journal of Geriatrics (Japan), 1996, 33/11 (840-846)

The diet in Japan has improved, but calcium intake has not increased for the past ten years, and it remains insufficient. To prevent osteoporosis, instruction in nutrition is directed at increasing calcium intake. We studied the effect of measuring bone mineral density on calcium intake in people receiving nutrition education. Intake of other nutrients was also measured. The subjects were 87 healthy women living in an agricultural region (Yamanashi Prefecture). They were members of a group formed to improve the diet of people in their area. For three days in October 1992 and in August 1994 food-weight records were obtained. A total of 76 of the 87 women chose to have their bone mineral density measured. The measurements before the first nutrition assessment in 1992. The intake of almost all nutrients tended to be greater in 1994 than in 1992. Calcium intake exceeded the minimum daily requirement (600mg). Calcium intake increased between 1992 and 1994 only in the subjects whose bone mineral density had been measured. Calcium intake decreased in the other subjects. Therefore, nutrition education programs aimed at preventing osteoporosis may be more

effective if bone mineral density is measured. In addition, an appropriate balance of other nutrients can be maintained as the intake of calcium is increased.

Osteoporosis: Its pediatric causes and prevention opportunities

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Primary Care Update for Ob/Gyns (USA), 1997, 4/1 (15-20)

Osteoporosis is the most common metabolic bone disease in western societies, and is characterized by a reduction of bone mass leading to the increased susceptibility to fractures. With increases in life expectancy and in the number of elderly people, bone loss and fractures are becoming more common in the United States and throughout the world. As a consequence, an epidemic of bone fractures among the elderly is expected. In this respect, it is obvious that the emphasis should be on the development of strategies for maximizing bone gain and preventing bone loss and subsequent osteoporosis. This paper discusses the concepts that are the foundation for primary prevention of osteoporosis: the measures that should be implemented during childhood and adolescence, with the goal of optimizing bone mass in young adulthood. Some important concepts, such as peak bone mass and calcium intake threshold, as well as the original studies of adolescent females and their bone mass acquisition are presented. It becomes clear that osteoporosis could have its roots during growth, and it should be treated as such. Teenagers should therefore be targeted as a population at risk, and preventive measures should be implemented by means of adequate calcium intake, proper diet, and exercise programs aimed at increasing peak bone mass.

Estimated dietary calcium intake and food sources for adolescent females: 1980-92

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Journal of Adolescent Health (USA), 1997, 20/1 (20-26)

Purpose: To estimate dietary calcium intake of three groups of adolescent females ages 11-12 years, 13-14 years, and 15-18 years during four separate 2-year time periods from the years 1980-92; and to identify their food sources of calcium.

Methods: Nutrient intake survey based on 14-day food consumption records collected from four national representative samples of 4,000 United States households.

Results: Dietary calcium consumption declined significantly ($p < .01$) over the 10-year period for the 15-18 year olds. Calcium intake was significantly lower for 13-14 year olds compared to the youngest age group, and for 15-18 year olds

when compared to the two younger age groups for all four study periods ($p < .01$). Over 90% of all adolescent females consumed < 100% of the RDA for calcium during all data collection periods. The percentage of adolescent females who consumed less than two- thirds of the RDA increased with age. Seventy-seven percent of 15-18 year olds consumed below this level from 1990-92. Milk and milk products were the best food sources of calcium contributing over one-half of the calcium to the diet. This percentage declined over time and with age to 44% for the 15-18 year old females in 1990. This drop can be attributed to a 7-12% decline in fluid milk consumption for the 11-12 year olds and 15-18 year olds, respectively.

Conclusions: Estimates indicate that dietary calcium intakes fall far short of both the Recommended Dietary Allowance (RDA) and National Institutes of Health (NIH) recommendations. Intakes have declined over time, with age, and appear to be related to a decline in fluid milk consumption. Efforts to increase calcium consumption among adolescent females appear critical. Clear recommendations to consume a minimum of three servings everyday of lowfat or nonfat dairy products such as milk and yogurt are needed to help this population meet daily calcium requirements.

The importance of genetic and nutritional factors in responses to vitamin D and its analogs in osteoporotic patients

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Calcified Tissue International (USA), 1997, 60/1 (119-123)

The effects of vitamin D and its analogs on fractures and bone mass have been clarified by clinical observations for more than 10 years. Reviewing the results of six clinical trials on osteoporotic fractures using activated vitamin D analogs, there appeared to be a negative correlation between basal levels of calcium intake and the incidence of vertebral fractures in the control groups. For example, when daily calcium intake was about 600 mg, there were approximately 800 vertebral fractures per 1000 persons a year in the controls. When daily calcium intake was above 1000 mg, the incidence was less than 400 fractures per 1000 persons a year. The incidence of fractures de-creased by about half in the activated vitamin D-treated group compared with the control group, but the most marked preventive effects of activated vitamin D on fractures were obtained in clinical studies, with daily calcium intakes of 400-800 mg. The effects of vitamin D analogs on bone mass were reported in the clinical studies, but the results are not consistent. However, these studies suggest that the effects of both 1,25(OH)2D3 and 1-alpha(OH)D3 on bone mass were dose dependent, and the doses were low in clinical studies in which good results were not obtained. Significant effects on bone mass were obtained when more than 0.6 microg of 1,25(OH)2D3, or more than 0.75 microg of 1-alpha(OH)D3 was administered, with increase in the urinary calcium level being within the acceptable range. Reported data indicate that both nonactivated vitamin D and activated vitamin D reduce the serum

parathyroid hormone level. However, activated vitamin D administration is more effective, and is able to reduce bone resorption in postmenopausal, osteoporotic patients with a vitamin D-sufficient status. Recent studies concerning the polymorphism of the vitamin D-receptor gene emphasize that sensitivity to active vitamin D varies between genotypes. In the bb type, sensitivity to active vitamin D is high, and calcium absorption efficiency in the intestine under low calcium conditions increases with increase in the serum 1,25(OH)2D level. A significant increase in lumbar bone mineral density was obtained after administration of activated vitamin D to osteoporotic patients of bb type. However, in the genotype with the B factor, sensitivity to active vitamin D was low, and the rate of increase of bone density was low. These data suggest that nutritional and genetic factors are critical when using active vitamin D and its analogs in the treatment of osteoporosis.

The pathogenesis of age-related osteoporotic fracture: Effects of dietary calcium deprivation

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Journal of Clinical Endocrinology and Metabolism (USA), 1997, 82/1 (260-264)

The pathogenesis of osteoporotic fracture after the menopause is uncertain. We studied the effects of a 4-day low calcium diet on 17 subjects with vertebral osteoporotic fracture and 17 age-matched controls with a bone density within the young normal range and without fracture. At baseline, the osteoporotic patients were well matched to normal subjects in terms of calcium intake and absorption and renal function, but had higher bone turnover and relative secondary hyperparathyroidism. After the low calcium diet, the rise in calcitriol was deficient in the osteoporotic subjects. These data are consistent with the suggested pathogenesis of type II or age- related osteoporosis and show that in these subjects with osteoporotic fracture there was a primary defect in calcitriol production that resulted in secondary hyperparathyroidism. This defect may be the cause of the high bone turnover and may play an important role in the development of bone loss in these subjects.

Increased catabolism of 25-hydroxyvitamin D in patients with partial gastrectomy and elevated 1,25-dihydroxyvitamin D levels. Implications for metabolic bone disease

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Journal of Clinical Endocrinology and Metabolism (USA), 1997, 82/1 (209-212)

Serum vitamin D metabolites and PTH were measured in seven subjects with a history of previous partial gastrectomy (PGX) and metabolic bone disease. The elimination tone-quarter of (3H)25-hydroxyvitamin D3 ((3H)25OHD3) in serum was assessed after an iv pulse dose of 5 microCi (26,27-3H)25OHD3. Median serum 25OHD3 was 37.5 (27.5-101.3) nmol/L, (normal range (NR) 10.8-58.5 nmol/L), mean serum 1,25-dihydroxyvitamin D (1,25-(OH)2D3) was raised at 175 + or - 72 pmol/L, (NR 48-120 pmol/L) and mean PTH was also high, 67 + or - 27 ng/L, (NR 10- 60 ng/L). Serum tone-quarter (3H)25OHD3 ranged from 10.9-21.2 days. A strong negative correlation existed between tone-quarter (3H)25OHD3 and serum 1,25- (OH)2D3 (Spearman's rank correlation coefficient ($r = -0.82$, $P = 0.002$)) and PTH) Spearman's rank correlation coefficient ($r = -0.81$, $P = 0.001$)). Four subjects who had high initial PTH concentrations (60-115 ng/L) and elevated 1,25-(OH)2D levels (162300 pmol/L) were reassessed after calcium supplementation to suppress secondary hyperparathyroidism (2degreeHPT). In this subgroup, after-treatment PTH fell from 82 + or - 24 to 52 + or B 24 ng/L (mean plus or minus SD), not significant; 1,25-(OH)2D fell from 210 plus or minus 61 to 116 plus or minus 28 pmol/L, $P = 0.015$; and tone-quarter (3H)25OHD3 increased from 13.2 + or - 1.9 to 18.9 plus or minus 3.1 days, $P = 0.012$. Patients with PGX and evidence of 2degreeHPT with elevated 1,25(OH)2D have a reduced tone-quarter (3H)25OHD3, and this may explain the increased susceptibility of the subjects to osteomalacia. Calcium supplementation suppresses 2degreeHPT, increases tone-quarter (3H)25OHD3 and may protect against PGX osteoporosis and osteomalacia.

Can the fast bone loss in osteoporotic and osteopenic patients be stopped with active vitamin D metabolites?

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Calcified Tissue International (USA), 1997, 60/1 (115-118)

The aim of this study was to evaluate whether fast trabecular bone loss in osteoporotic and osteopenic patients can effectively be treated with active vitamin D metabolites. Thirty-one osteoporotic and osteopenic patients were monitored between 4 and 22 months before and between 8 and 18 months during the treatment. Fast bone losers were designated as osteoporotic or osteopenic patients with a loss of trabecular bone density in the radius of 3% or more calculated for 1 year. For this differentiation, the high precise peripheral quantitative computed tomography system (DENSISCAN 1000) was used (reproducability 0.3% in mixed collectives). The pretreatment loss and the 'gain' under treatment with active vitamin D metabolites was calculated for 1 year. The treatment consisted of either 0.5 microg calcitriol daily or 1 microg of alfacalcidol daily. Before treatment, the trabecular bone loss in the radius/ year was -6.6 + or - 0.5% (mean + or - SEM). After treatment with vitamin D metabolites, the trabecular bone gain in the radius/year was 0.01 + or - 0.6% (mean + or - SEM). The difference was highly significant ($P < 0.001$). In contrast to this, the loss of cortical bone density before treatment was -1.8 + or - 0.3% (mean + or - SEM) and the reduced loss

after treatment -0.2 + or - 0.4% (mean plus or minus SEM), both values calculated for 1 year. This difference was less significant ($P < 0.05$). This study shows that the treatment with active vitamin D metabolites is very effective in slowing fast trabecular bone loss in osteoporotic and osteopenic patients.

Is there a differential response to alfacalcidol and vitamin D in the treatment of osteoporosis?

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Calcified Tissue International (USA), 1997, 60/1 (111-114)

There is a decline in serum 25 hydroxyvitamin D (25OHD), 1,25 dihydroxyvitamin D (1,25(OH)2D), and calcium absorption with advancing age, which may lead to secondary hyperparathyroidism and bone loss. Studies show a relationship between serum 25OHD and bone density in older men and women, with an inverse correlation between bone density and parathyroid hormone (PTH). Vitamin D supplementation in this age group improves calcium absorption, suppresses PTH, and decreases bone loss. Vitamin D many also reduce the incidence of hip and other nonvertebral fractures, particularly in the frail elderly who are likely to have vitamin D deficiency. Patients with established vertebral osteoporosis have lower calcium absorption than age- matched control subjects, possibly due to reduced serum 1,25(OH)2D or to relative resistance to the action of vitamin D on the bowel. Malabsorption of calcium in women with vertebral crush fractures does not usually respond to treatment with physiological doses of vitamin D, but can be corrected by pharmacological doses of vitamin D or by low doses of calcitriol or alfacalcidol. In a recent randomized, controlled study in 46 elderly women with radiological evidence of vertebral osteoporosis, alfacalcidol 0.25 microg twice daily improved calcium absorption, decreased serum PTH, and reduced alkaline phosphatase, whereas vitamin D2 5001000 IU daily had no effect over the 6-month study period. Studies of the effect of the vitamin D metabolites in the management of elderly women with established vertebral osteoporosis have yielded conflicting results, but suggest that alfacalcidol and calcitriol may decrease spinal bone loss and reduce the incidence of vertebral fractures. Although vitamin D supplementation decreases bone loss and fracture risk in the frail elderly, vitamin D metabolites may prove more useful in the treatment of elderly women with vertebral osteoporosis.

Rationale for active vitamin D analog therapy in senile osteoporosis

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Calcified Tissue International (USA), 1997, 60/1 (100-105)

Osteoporosis is diagnosed when bone density decreases below the fracture threshold, a change that is associated with decreased biomechanical integrity and fracture. There are two types of primary osteoporosis: postmenopausal osteoporosis and senile osteoporosis. Postmenopausal osteoporosis is due to some combinations of a low peak bone density and a high rate of bone loss during the early postmenopausal years. The bone loss is primarily due to estrogen deficiency, which leads to increases in resorbing cytokines and a consequent increase in bone resorption. The pathogenesis of senile osteoporosis is less well understood and includes factors in addition to estrogen deficiency. A potential etiological factor is the vitamin D deficiency that occurs with advancing age. Severe vitamin D deficiency in the adult leads to osteomalacia, whereas a mild deficiency, which is common in the elderly, is rarely associated with mineralization defects but instead could lead to development of secondary hyperparathyroidism and osteoporosis. There are basically two types of vitamin D deficiency: (1) primary vitamin D deficiency which is due to a deficiency of vitamin D, the parent compound of the active metabolite 1,25(OH)2D3; and (2) a deficiency of 1,25(OH)2D3 action resulting from either decreased production of 1,25(OH)2D3 by the kidney or from decreased responsiveness to 1,25(OH)2D3 of target tissues, i.e., resistance. Both types of deficiencies could occur with aging, and both have been implicated as potential causes of senile osteoporosis. In this paper, we would like to advance the hypothesis that the age-related deficiency in 1,25(OH)2D3 action plays a role in the pathogenesis of senile osteoporosis. We will provide evidence to support the concept that a deficiency of 1,25(OH)2D3 action exists in the elderly, which plays a role in age-related bone loss, and that this deficiency of 1,25(OH)2D3 action can be successfully treated with 1,25(OH)2D3 or 1alpha-hydroxy vitamin D3 (1alpha(OH)D3).

Efficacy and safety of long-term, open-label treatment of calcitriol in postmenopausal osteoporosis: A retrospective analysis

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Current Therapeutic Research - Clinical and Experimental (USA), 1996, 57/11 (857-868)

To assess the efficacy and safety of calcitriol treatment in postmenopausal osteoporotic patients, a retrospective study was made of 340 women (mean age plus or minus SD, 63 plus or minus 7.7 years) with established postmenopausal osteoporosis characterized by calcium malabsorption who received long-term, open-label treatment with calcitriol 1 microg/d. The patients were separated into subgroups based on the length of calcitriol therapy (1 to 14 years). The previously reported data of 25 postmenopausal osteoporotic women (mean age + or - SD, 64 plus or minus 7.2 years), untreated for a period of 2 years, were used as a control group. Calcitriol promoted a significant increase in intestinal calcium absorption at all treatment durations, with no clinically significant changes in serum calcium or creatinine levels. Urinary calcium increased in a statistically significant manner

and was always higher than at baseline as long as calcitriol was administered, without modifying blood urea nitrogen and serum creatinine levels. Urinary hydroxyproline excretion was generally unchanged, indicating that the increased calcium excretion was due to increased intestinal absorption rather than bone catabolism. Measured by using a visual analog scale, pain decreased markedly and statistically significantly during treatment in all groups. There was a slight but progressive mean height loss during the study, although this was only 2 cm in the patients treated for 9 years or more. Measurements of bone mineral density (BMD) showed that both total body BMD and spine BMD were largely unchanged during treatment, whereas the decrease in BMD in the untreated osteoporotic patients was more than 2%. The occurrence of nontraumatic clinically relevant fractures decreased noticeably in comparison with the period preceding calcitriol treatment.

Magnesium deficiency: Possible role in osteoporosis associated with gluten-sensitive enteropathy

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Osteoporosis International (United Kingdom), 1996, 6/6 (453-461)

Osteoporosis and magnesium (Mg) deficiency often occur in malabsorption syndromes such as gluten-sensitive enteropathy (GSE). Mg deficiency is known to impair parathyroid hormone (PTH) secretion and action in humans and will result in osteopenia and increased skeletal fragility in animal models. We hypothesize that Mg depletion may contribute to the osteoporosis associated with malabsorption. It was our objective to determine Mg status and bone mass in GSE patients who were clinically asymptomatic and on a stable gluten-free diet, as well as their response to Mg therapy. Twenty-three patients with biopsy-proven GSE on a gluten-free diet were assessed for Mg deficiency by determination of the serum Mg, red blood cell (RBC) and lymphocyte free Mg2+, and total lymphocyte Mg. Fourteen subjects completed a 3-month treatment period in which they were given 504-576 mg MgCl2 or Mg lactate daily. Serum PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and osteocalcin were measured at baseline and monthly thereafter. Eight patients who had documented Mg depletion (RBC Mg2+ < 150 microM) underwent bone density measurements of the lumbar spine and proximal femur, and 5 of these patients were followed for 2 years on Mg therapy. The mean serum Mg, calcium, phosphorus and alkaline phosphatase concentrations were in the normal range. Most serum calcium values fell below mean normal and the baseline serum PTH was high normal or slightly elevated in 7 of the 14 subjects who completed the 3-month treatment period. No correlation with the serum calcium was noted, however. Mean serum 25-hydroxyvitamin D, 1,25-dihydroxy vitamin D and osteocalcin concentrations were also normal. Despite only 1 patient having hypomagnesemia, the RBC Mg2+ (153 + or - 6.2 microM; mean plus or minus SEM) and lymphocyte Mg2+ (182 plus or minus 5.5 microM) were significantly lower than normal (202 + or - 6.0 microM, P < 0.001, and 198 + or - 6.8 microM, p < 0.05, respectively). Bone

densitometry revealed that 4 of 8 patients had osteoporosis of the lumbar spine and 5 of 8 had osteoporosis of the proximal femur (T-scores less than or equal to -2.5). Mg therapy resulted in a significant rise in the mean serum PTH concentration from 44.6 + or - 3.6 pg/ml to 55.9 plus or minus 5.6 pg/ml ($p < 0.05$). In the 5 patients given Mg supplements for 2 years, a significant increased in bone mineral density was observed in the femoral neck and total proximal femur. This increase in bone mineral density correlated positively with a rise in RBC Mg^{2+}. This study demonstrates that GSE patients have reduction in intracellular free Mg^{2+}, despite being clinically asymptomatic on a gluten-free diet. Bone mass also appears to be reduced. Mg therapy resulted in a rise in PTH, suggesting that the intracellular Mg deficit was impairing PTH secretion in these patients. The increase in bone density in response to Mg therapy suggests that Mg depletion may be one factor contributing to osteoporosis in GSE.

Effects of vitamin B12 on cell proliferation and cellular alkaline phosphatase activity in human bone marrow stromal osteoprogenitor cells and UMR106 osteoblastic cells

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Metabolism: Clinical and Experimental (USA), 1996, 45/12 (1443-1446)

Pernicious anemia has recently been recognized as one of the risk factors for osteoporosis and bone fractures, but the underlying pathophysiologic mechanism is still unknown. To determine whether vitamin B12 has any direct effect on osteoblasts, we studied the effects of vitamin B12 on the proliferation and alkaline phosphatase activity in human bone marrow stromal osteoprogenitor cells (hBMSC) and UMR106 osteoblastic cells. Vitamin B12 at concentrations as low as 10-12 mol/L significantly stimulated (3H)-thymidine incorporation in both types of cells, but concentrations higher than 10-12 mol/L did not produce a greater effect.Vitamin B12 in the concentration range from 10-12 to 10-8 mol/L concentration- dependently increased alkaline phosphatase activity in both hBMSC and UMR106 cells. Based on these results, we suggest that a suppressed activity of osteoblasts may contribute to osteoporosis and fractures in patients with vitamin B12 deficiency.

Calcium metabolism in the elderly

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Giornale di Gerontologia (Italy), 1996, 44/2 (91-96)

The aging process is characterized by several alterations in calcium metabolism and by a negative calcium balance. Total body calcium is reduced in the elderly. Since 99% of total body calcium is localized in the bone this reduction is associated with a reduction in progressive bone mass, increased fragility of the skeleton, and with increased risk of fractures. The reduction in calcium with aging is paradoxically associated with an accumulation of calcium within the cells and soft tissues. From a metabolic point of view, the aging process is associated with several alterations in calcium homeostasis. Calcium intake, calcium absorption, and renal calcium conservation are all reduced in the aged. Calciotropic hormone levels undergo alterations with age. 25(OH)2 levels tend to decrease with age due to reduced vitamin D intake and as a result of a reduction in exposure to the sun. PTH levels in response to the status of calcium deprivation and the reduction of serum ionized calcium progressively tend to increase with age. Aging is also associated with an increase in bone turnover, as documented by the increased levels of the serum and urinary markers of bone formation and bone reabsorption. This increase in bone remodeling is directly related to the reduction in bone mass and the increased risk of fractures. Calcium supplements together with drugs able to reduce bone turnover, may contribute to the normalizing of the calcium balance, and reducing the risk of fractures in the elderly.

Hormones, vitamins, and growth factors in cancer treatment and prevention: A critical appraisal

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Cancer (USA), 1996, 78/11 (2264-2280)

BACKGROUND. Hormones, hormone agonists, hormone antagonists, vitamins and their synthetic analogues, and growth factors are currently the most widely used anticancer drugs. Although in many cases they provide dramatic results, in other cases their effects are conflicting. A critical appraisal of the effects of these drugs is needed.

METHODS. To evaluate the potential therapeutic and preventive roles of these drugs as well as their areas of controversy, data published in the literature in the last two decades are reviewed in this article, and the author's personal findings are also reviewed.

RESULTS.Hormones, hormone agonists, hormone antagonists, vitamins and their synthetic analogues, growth factors, and cytokines are replacing conventional cancer therapies (chemotherapy, surgical therapy, and radiation therapy) for many purposes, and recently became the 'fourth arm' of cancer treatment. However, their mechanisms of action have not yet been elucidated. This article critically reviews the mechanisms of their action on cancer cells (specifically, DNA, RNA, oncogenes, and antioncogenes); their role in cancer cell division, cell cycle, apoptosis, and angiogenesis; and their relation to human cancers. Since hormones,

vitamins, growth factors (GFs), and GF receptors play a cardinal role in multistage carcinogenesis, using monoclonal antibodies to develop novel hormone antagonists, vitamin synthetic analogues, and GF inhibitors will be of paramount significance for neoadjuvant systemic therapy and cancer prevention.

CONCLUSIONS. It is hoped that the data presented in this review regarding the role of hormones, hormone agonists, hormone antagonists, vitamins, growth factors, and growth factor inhibitors will provide a rationale for designing effective new cancer chemoprevention strategies and clinical trials.

Therapy of osteoporosis: Calcium, vitamin D, and exercise

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American Journal of the Medical Sciences (USA), 1996, 312/6 (278-286)

Calcium supplementation has long been regarded as a fundamental part of the prevention and treatment of postmenopausal osteoporosis, but it is only in recent years that clear evidence has emerged demonstrating its impact on bone mass. Calcium supplementation does not completely arrest postmenopausal bone loss but slows the rate of decline by 30 to 50%. The effect of calcium supplementation on fracture incidence in postmenopausal women has not been established. Vitamin D deficiency is common in the frail elderly, particularly in countries where fortification or food with this vitamin is not practiced. Treatment of vitamin D deficiency has been associated with significant reductions in the number of hip fractures. The role of the potent vitamin D metabolites, calcitriol and alphacalcidol, in the management of postmenopausal osteoporosis is not clear. Although some studies show substantial benefits in bone density or fracture rate from the use of these compounds, the published data are inconsistent. In general, hormone replacement therapy and the potent bisphosphonates produce greater effects on bone density and there is a greater consistency among the results of the published studies of these other interventions. Controlled trials of exercise interventions in postmenopausal women show that exercise can positively influence bone density by a few percent. Exercise interventions in the elderly have been reported to decrease fall frequency by 10%. This latter effect may have a greater impact on fracture frequency than the modest benefits of exercise on bone density.

Pathophysiology of osteoporosis

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American Journal of the Medical Sciences (USA), 1996, 312/6 (251-256)

As with many chronic diseases that express themselves late in life, osteoporosis is distinctly multifactorial both in etiology and in pathophysiology. Osteoporotic fractures occur because of a combination of injury and intrinsic bony fragility. The injury comes most often from a combination of falls, poor postural reflexes that fail to protect bony parts from impact, and reduced soft tissue padding over bony prominences. The bony fragility itself is a composite of geometry, low mass density, severance of microarchitectural connections in trabecular structures, and accumulated fatigue damage. Reduced bone mass, in turn, is caused by varying combinations of gonadal hormone deficiency, inadequate intakes of calcium and vitamin D, decreased physical activity, comorbidity, and the effects of drugs used to treat various unrelated medical conditions. Finally, the often poor outcome from hip fracture in the elderly is partly caused by associated protein- calorie malnutrition. An adequate preventive program for osteoporotic fracture must address as many of these factors as possible, ie, it must be as multifaceted as the disease is multifactorial.

Involutional osteoporosis in the elderly

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Involutional osteoporosis (IO) is a multifactorial disorder resulting in bone fragility and fractures due to bone loss. Estrogen deficiency is known to be a dominant contributor to the postmenopausal bone loss. The mode of action of estrogen on bone tissue has been recently clarified by the demonstration of estrogen receptors in bone cells suggesting a direct effect of estrogens on bone tissue. However, over the years, other theories have been proposed to explain the pathophysiological mechanism underlying IO. These involve the calcium regulating hormones: calcitonin (CT), vitamin D metabolites and parathyroid hormone (IPTH). Studies have shown that women have lower serum CT levels, decreased secretory reserve than men, and that estrogens can increase CT secretion in pre- and postmenopausal women. Another important determinant of postmenopausal bone loss is an impaired intestinal calcium absorption. This phenomenon appears to be the result of two defects: increased intestinal resistance to 1,25 (OH)2D3 action and, later in life, impaired conversion of 25 (OH)D to 1,25 (OH)2D. A third hypothesis to explain estrogen effect on bone suggests that estrogens may modulate the sensitivity of bone to PTH-induced bone resorption. Several studies have shown that PTH activity increases with age. This finding is the probable cause of the increase in bone turnover rate and, because of the coexistence of an age-related imbalance in bone remodeling, would lead to increase bone loss. Finally, recent studies have shown that some local factors, such as citokines and skeletal growth factors may play a role in the control of bone remodeling and bone loss.

Dietary calcium intake and its relation to bone mineral density in patients with inflammatory bowel disease

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Journal of Internal Medicine (United Kingdom), 1996, 240/5 (285-292)

Objectives. To investigate calcium intake and its association with bone mineral density (BMD) and the type and extent of the disease in patients with inflammatory bowel disease (IBD).

Setting. University hospital clinic.

Subjects. A total of 152 unselected IBD patients and 73 healthy controls.

Measurements. Dietary calcium intake was assessed with a food frequency questionnaire and BMD of the lumbar spina and proximal femur was measured.

Results. The IBD patients had lower dietary calcium intake (1034 (SD 493) mg) than the controls (1334 (514) mg, $P < 0.001$). The difference was significant in the males (1047 (552) mg and 1575 (586) mg, respectively, $P < 0.001$), but not in the females (1020 (422) mg and 1112 (303) mg). The dietary daily calcium intake was below 1000 mg in 53% of the patients and 27% of the controls ($P = 0.0004$) and below 400 mg in 9.2% of the patients and none of the controls ($P = 0.007$). The calcium intake was not associated with the severity or the type of IBD. Seventy-one (47%) patients and eight (11%) controls avoided lactose in their diet ($P < 0.001$). In the IBD patients, no association between the calcium intake and BMD was detected, whereas in the controls a positive correlation between the calcium intake and the BMD of the proximal femur was found.

Conclusions, Calcium intakes below the recommendations are seen more often in the IBD patients than in the healthy controls, but in the IBD patients the calcium intake is not associated with BMD in a cross-sectional study. A low-lactose diet is common among IBD patients. To reduce the risk of inadequate calcium intake, unnecessary dietary restrictions concerning, e.g. milk products, should be avoided for these patients.

Clinical practice guidelines for the diagnosis and management of osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/8 (1113-1129)

Objective: To recommend clinical practice guidelines for the assessment of people at risk for osteoporosis, and for effective diagnosis and management of the condition.

Options: Screening and diagnostic methods: risk-factor assessment, clinical evaluation, measurement of bone mineral density, laboratory investigations.

Prophylactic and corrective therapies: calcium and vitamin D nutritional supplementation, physical activity and fall-avoidance techniques, ovarian hormone therapy, bisphosphonate drugs, other drug therapies. Pain-management medications and techniques.

Outcomes: Prevention of loss of bone mineral density and fracture; increased bone mass; and improved quality of life.

Evidence: Epidemiologic and clinical studies and reports were examined, with emphasis on recent randomized controlled trials. Clinical practice in Canada and elsewhere was surveyed. Availability of treatment products and diagnostic equipment in Canada was considered.

Values: Cost-effective methods and products that can be adopted across Canada were considered. A high value was given to accurate assessment of fracture risk and osteoporosis, and to increasing bone mineral density, reducing fractures: and fracture risk and minimizing side effects of diagnosis and treatment.

Benefits, harms and costs: Proper diagnosis and management of osteoporosis minimize injury and disability, improve quality of life for patients and reduce costs to society. Rationally targeted methods of screening and diagnosis are safe and cost effective. Harmful side effects and costs of recommended therapies are minimal compared with the harms and costs of untreated osteoporosis. Alternative therapies provide a range of choices for physicians and patients.

Recommendations: Population sets at high risk should be identified and then the diagnosis confirmed through bone densitometry. Dual-energy x-ray absorptiometry is the preferred measurement technique. Radiography can be an adjunct when indicated. Calcium and vitamin D nutritional supplementation should be at currenly recommended levels. Patients should be counselled in fall-avoidance techniques and exercises. Immobilization should be avoided. Guidelines for management of acute pain are listed. Ovarian hormone therapy is the therapy of choice for osteoporosis prevention and treatment in post menopausal women. Bisphosphonates are an alternative therapy for women with established osteoporosis who cannot or prefer not to take ovarian hormone therapy.

Validation: These guidelines were reviewed and approved by the Scientific Advisory Board of the Osteoporosis Society of Canada, in consultation with individual family and general practitioners.

Vitamin D metabolites and analogs in the treatment of osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/7 (955-961)

Objective: To review recent findings on the skeletal actions of vitamin D and to examine results of the latest clinical trials of vitamin D in the treatment of osteoporosis.

Options: The vitamin D analog 1-alpha hydroxycholecalciferol (1alpha-OH-D3); the vitamin D metabolite calcitriol.

Outcomes: Fracture and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures and improved quality of life associated with vitamin D therapies.

Evidence: Relevant laboratory and clinical studies and reports were examined. Greatest reliance was placed on recent large-scale, randomized, controlled trials; others were noted and their methods critiqued. Clinical practice in Japan was also considered.

Values: Reducing fractures, increasing bone mineral density and minimizing side effects of treatment were given a high value. Benefits, harms and costs: Vitamin D maintains the dynamic nature of bone and so presumably helps to keep it healthy. Calcitriol and 1alpha-OH-D3 may be effective in increasing bone mass and preventing fractures in osteoporosis. Calcitriol may be an alternative treatment in the prevention and management of corticosteroid-induced osteoporosis. Possible side effects of vitamin D analogs and metabolites are hypercalcemia, hypercalciuria, renal calcification and renal stones.

Recommendations: The use of 1alpha-OH-D3 for the treatment of osteoporosis in Canada cannot be supported without larger and longer randomized, controlled clinical trials. Calcitriol appears to prevent vertebral fractures in patients with osteoporosis. More information is needed on its mechanism of action and efficacy in preventing hip fractures. Future studies should focus on comparisons with other effective therapies and on determining whether its effect on fractures is greater than that achieved through improved vitamin D nutrition. Patients taking calcitriol at dose levels required for antifracture effects should be monitored for serum and urine calcium response to the drug. Calcitriol should not be given to atients whose calcium intake is at current generally recommended levels. At present, prescription of calcitriol for the treatment of osteoporosis should be reserved for physicians with a special interest in the treatment of metabolic bone disease.

Validation: These recommendations were developed by the Scientific Advisory Board of the Osteoporosis Society of Canada at its 1995 Consensus Conference.

Calcium nutrition and osteoporosis

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Canadian Medical Association Journal (Canada), 1996, 155/7 (935-939)

Objective: To recommend appropriate levels of calcium intake in light of the most recent studies.

Options: Dietary calcium intake, calcium supplementation, calcium and vitamin D supplementation; ovarian hormone therapy in postmenopausal women.

Outcomes: Fracture and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures and improved quality of life associated with osteoporosis prevention.

Evidence: Relevant clinical studies and reports were examined, in particular those published since the 1988 Osteoporosis Society of Canada position paper on calcium nutrition. Only studies in humans were considered, including controlled, randomized trials and prospective studies, using bone mass and fractures as end-points. Studies in early and later phases of skeletal growth were noted. The analysis was designed to eliminate menopause as a confounding variable.

Values: Preventing osteoporosis and maximizing quality of life were given a high value. Benefits, harms and costs: Adequate calcium nutrition increases bone mineral density during skeletal growth and prevents bone loss and osteoporotic fractures in the elderly. Risks associated with high dietary calcium intake are low, and a recent study extends this conclusion to the risk of kidney stones. Lactase-deficient patients may substitute yogurt and lactase-treated milk for cow's milk. True milk allergy is probably rare; its promotion of diabetes mellitus in susceptible people is being studied.

Recommendations: Current recommended intakes of calcium are too low. Revised intake guidelines designed to reduce bone loss and protect against osteoporotic fractures are suggested. Canadians should attempt to meet their calcium requirements principally through food sources. Pharmaceutical calcium supplements and a dietician's advice should be considered where dietary preferences or lactase deficiency restrict consumption of dairy foods. Further research is necessary before recommending the general use of calcium supplements by adolescents. Calcium suplementation cannot substitute for hormone therapy in the prevention of postmenopausal bone loss and fractures. Adequate amounts of vitamin D are necessary for optimal calcium absorption and bone health. Elderly people and those who use heavy sun screens should have a dietary intake of 400 to 800 IU of vitamin D per day.

Interrelationships of food, nutrition, diet and health: The national association of state universities and land grant colleges white paper

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Nutrition and food science have each enhanced the development of an abundant, nutritious, safe food supply. A healthy diet should contain all of the required nutrients and sufficient calories to balance energy expenditure and provide for growth and maintenance throughout the life cycle. Importantly, dietary factors are associated with 5 of the 10 leading causes of death, including coronary heart disease, certain types of cancer, stroke, noninsulin dependent diabetes mellitus and atherosclerosis. National health care expenditures for 1990 totaled $666 billion of which 30% are related to inappropriate diet. Identification of external factors that contribute to premature death would aid preventive efforts, improve the quality of life, and reduce health care costs. Even though genetic predisposition increases susceptible people's risk for many of these chronic diseases, these conditions may be diminished or prevented by improvements in the American diet. Each stage of the life cycle has specific nutrient needs. Throughout infancy, childhood and adolescence nutrients are requited to meet the growth processes as well as cognitive function. During pregnancy nutrients are required for both mother and developing infant needs. Adult nutrition focuses on tissue maintenance, nutrient and energy needs, and disease prevention. As the population of elderly increase in number and greater age, nutritional needs must be met to minimize certain disease states and assure the quality of life. Nutrition associated health risks have been identified for coronary heart disease, cancer and diabetes mellitus. Recommendations for each includes a decrease in dietary fat, awareness of caloric intake and enhancement of nutrient density including an increase in fruit and vegetables. These recommendations also impact obesity and diminish the compounding of other disease states affected by excessive body weight. Calcium intake at early ages affects development of bone density and manifestation of osteoporosis. Current gaps in knowledge are also ientified that could improve health. Numerous nutrients are being examined for their regulation of specific gene expressions and in the processes of transcription and translation. To offer food products with greater nutrient density or improved functional health ingredients, modification of existing foods is needed to assure an improved diet. Policies to improve health require integration of nutrition needs with economic growth and development, agriculture and food production, processing, marketing, health care and education, and includes changing life styles and food choices. Increased research support is required to achieve national health goals with emphasis on nutrition and food sciences. Education methods must be improved to better inform consumers, to encourage food producers and manufacturers to produce healthier foods, to assure training of future professionals and to provide legislators with the basis to make informed decisions. Recommendations to CFERR aye identified. Improved quality and availability of nutritious foods will result in a healthier, more productive population. A decrease in the occurrence and duration of chronic diseases should diminish the cost of health care and allow

these resources to further benefit the nation. International concerns about undernutrition include 780 million people who are malnourished, lacking sufficient food to meet their basic nutritional needs for protein and energy, and 2 billion people who subsist on diets lacking essential nutrients needed for growth, development and physiological maintenance. National concerns about undernutrition exist based on incomplete data identified by indices of hunger and characterized by an increased demand for food assistance for women, children and the elderly. Major health problems in the US impacted by diet and nutrition include coronary heart disease, atherosclerosis, some types of cancer, non-insulin dependent diabetes mellitus, hypertension, hyperlipidemia, osteoporosis and obesity. Conservative estimates suggest improved nutriion could reduce health care costs by 10% (or more), potentially saving the US $15-20 billion annually. The disciplines of food science and nutrition can provide the means to carry out research, enhance education (train professionals and educate the public), and contribute to improved public policy.

Effect of Vitamin D receptor gene polymorphism on vitamin D therapy for postmenopausal bone loss

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Acta Obstetrica et Gynaecologica Japonica (Japan), 1996, 48/9 (799-805)

In order to assess the effect of vitamin D receptor (VDR) gene polymorphisms on vitamin D3 therapy for postmenopausal bone loss. Thirty-four Japanese postmenopausal women, administer ed vitamin D3 (Alfarol(R)1.0microg/day) and Ca(2.0g/day) for 18 months, were analyzed by RFLP Bone mineral density (BMI) at the lumbar spine (L2-4) and Os-calcis were measured every 6 months by dual energy X-ray absorptiometry (DXA) and single energy X-ray absorptiometry (SXA) VDR gene allelic polymorphisms were assessed by Bsm 1 endonuclease restriction after specific PCR amplification. Genotypic polymorphism was defined as BB, bb and Bb. The genotypes were BB in 1 (3.1%) Bb in 13 (40.6%) and bb in 18 (56.3%). The women in these two major VDR genotype groups (Bb and bb) were similar in their backgrounds (interms of age, menopausal age, body mass index, and BMD in premedication), but the VDR genotype was associated the percent of change in BMD after treatment. In Group-Bb, the mean percent increases in L2-4 BMD were 3.2%, 4.9% and 4.1% at 6, 12 and 18 months. In contrast, in Group-bb they were 0.8%, 1.8% and 4.2% at the same points. Analysis of VDR alleles may prove useful in selecting the vitamin D therapy for osteopenia before treatment.

The preparation and stability of compound active calcium tablets

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Chinese Pharmaceutical Journal (China), 1996, 31/8 (474-477)

Objective: To prepare compound active calcium tablets and evaluate their stability.

Method: The optimal formulation of the tablets was found with orthogonal experiment design. The stability of the tablets was investigated by shelf-life and accelerated experiment.

Results: The prepared tablets rapidly disentigrated in 15 min, and showed good stability under various experimental conditions.

Conclusion: The compound active calcium tablets will play an important part in prevention and treatment of late middle age or older osteoporosis.

Nutrition and women's health

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Current Problems in Obstetrics, Gynecology and Fertility (USA), 1996, 19/4 (112-166)

With the rapid changes that are occurring in our health care system, interventions that enhance patients' health will prove to be the most satisfactory and provide the most cost savings over time. Data support a strong relationship between diet and health and disease. Although life expectancy in the United States is increasing in women, longevity is also associated with increasing morbidity. As a nation, we may live longer, but not necessarily better, lives. Dietary modification can improve health and reduce disease incidence; thus advice on good nutrition and appropriately selected vitamin and mineral supplements becomes paramount. Because women are the primary providers of meals to their families, a woman's food selections have an impact not only on her health but also on the health of her entire family. Accumulating evidence suggests that maternal nutrition, intrauterine events, birth weight and weight at 1 year of age all have an impact on adult morbidity and mortality. In females, body weight and body composition affect sexual maturation, onset of menstruation, ovulation, and fertility. With pregnancy, further body compositional changes occur with increased deposition of fat stores, especially in the hips and thighs. Recurring pregnancy, a sedentary lifestyle, and an abundance of food contribute to obesity, which is on the rise in the United States. With menopause, a decline in fat-free mass, bone mass, and lean tissue occurs. This loss in lean tissue includes not only muscle but also neuronal and connective tissue. Furthermore, with menopause fat is redistributed in the body with an increase in truncal deposition of adipose tissue, which is associated with an increased risk of coronary heart disease (CHD) and breast

cancer. These risk factors can be attenuated through appropriate diet, hormone replacement therapy, and exercise, which emphasizes resistance training. One approach to an appropriate diet would focus on 'culturally based' dietary patterns. A Mediterranean-based diet, an Asian- based diet, or othr ancestral-based diets have recently been suggested. These dietary patterns are associated with the decreased incidence of many chronic diseases and the maintenance of long-term health. The type of fat in the diet influences many aspects of health. Saturated fats, whether derived from animal or vegetable sources, are associated with increased risk for cardiovascular disease and certain cancers. Fats derived from fish oils appear to be cardioprotective and are associated with decreased incidence of breast cancer in epidemiologic and animal studies. Monounsaturated fats, such as those found in olive oil, appear to decrease serum triglycerides and may reduce the risk for breast cancer. A greater consumption of vegetables and fruit is associated with a decreased incidence of heart disease and many types of cancer. The protective factors in plant-derived foods include fiber, folic acid, antioxidant vitamins, carotenoids, and nonnutritive chemoprotective factors such as genistein, deidzen, and lignans. Plant- derived foods are also high in magnesium and calcium, which are associated with cardioprotection, reduced risk for certain cancers, and attenuation of osteoporosis. The ideal diet is based on the eating habits of our ancestors. It emphasizes the use of unrefined food products and drastically reduces the consumption of highly processed flours and grains and simple sugars that are added to most foods. Optimal recommendations include the daily consumption of large amounts of fresh fruits and vegetables. Animal-based protein would be replaced with plant protein and fish. Selective supplementation with vitamins and minerals would be encouraged for patients who are unwilling or unable to modify their eating habits and where scientific data support their use.

Current treatment options for osteoporosis

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The goals of treatment for patients with osteoporosis are to maintain normal bone and to prevent the deterioration of normal bone to osteoporotic bone. Achievement of these goals, combined with a successful approach to prevention of falls, may substantially decrease the incidence and risk of fractures. Strategies for osteoporosis therapy include patient strategies (e.g., administration of calcium, exercise), drug therapy to stimulate bone formation (e.g., fluoride, anabolic steroids), and drugs to inhibit bone resorption (e.g., estrogen replacement therapy, calcitonin, bisphosphonates).

A comparison of the effects of alfacalcidol treatment and vitamin D2 supplementation on calcium absorption in elderly women with vertebral fractures

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Osteoporosis International (United Kingdom), 1996, 6/4 (284-290)

Although vitamin D supplementation in the frail elderly improves calcium absorption, suppresses parathyroid hormone, decreases bone loss and reduces the risk of fractures, such treatment may be ineffective in patients with vertebral osteoporosis, because of impaired vitamin D metabolism or resistance to the action of vitamin D metabolites on the bowel. We have therefore performed a randomized, single masked study comparing the effects of alfacalcidol treatment (0.25 microg twice daily) and vitamin D2 supplementation (500-1000 units daily) on calcium absorption and bone turnover in 46 elderly women (median age 69 years, range 64-79 years) with radiological evidence of vertebral fractures. Serum 25-hydroxyvitamin D increased significantly after 3 and 6 months of treatment with vitamin D2 ($p < 0.001$), but was unchanged in the group receiving alfacalcidol. Serum 1,25-dihydroxyvitamin D did not change significantly in either group over the study period. Fractional 45Ca absorption increased after 3 months of treatment with alfacalcidol ($p < 0.05$), but was unchanged with vitamin D2. There was also a reduction in plasma intact parathyroid hormone and serum alkaline phosphatase after 6 months of treatment with alfacalcidol ($p < 0.05$) which was not seen in the group receiving vitamin D2. Our study shows that vitamin D2 supplementation is ineffective in stimulating calcium absorption in elderly women with vertebral osteoporosis. By increasing calcium absorption in such patients, alfacalcidol may prove more effective than vitamin D in the management of vertebral osteoporosis.

The effect of calcium supplementation and Tanner Stage on bone density, content and area in teenage women

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One hundred and twelve Caucasian girls, 11.9 + or - 0.5 years of age at entry, were randomized into a 24-month, double-masked, placebo-controlled trial to determine the effect of calcium supplementation on bone mineral content, bone area and bone density. Supplementation was 500 mg calcium as calcium citrate

malate (CCM) per day. Controls received placebo pills, and compliance of both groups averaged 72%. Bone mineral content, bone mineral area and bone mineral density of the lumbar spine and total body were measured by dual energy X-ray absorptiometry (DXA). Calcium intake from dietary sources averaged 983 mg/day for the entire study group. The supplemented group received, on average, an additional 360 mg calcium/day from CCM. At baseline and after 24 months, the two groups did not differ with respect to anthropometric measurements, urinary reproductive hormone levels or any measurement of pubertal progression. The supplemented group had greater increases of total body bone measures: content 39.9% versus 35.7% ($p = 0.01$), area 24.2% versus 22.5% ($p = 0.15$) and density 12.2% versus 10.1% ($p = 0.005$). Region-of-interest analyses showed that the supplemented group had greater gains compared with the control group for bone mineral density, content and area. In particular, in the lumbar spine and pelvis, the gains made by the supplemented group were 12%-24% greater than the increases made by the control group. Bone acquisition rates in the two study groups were further compared by subdividing the groups into those with below- or above-median values for Tanner score and dietary calcium intake. In subjects with below-median Tanner scores, bone acquisition was not affected by calcium supplementation or dietary calcium level. However, the calcium supplemented subjects with above-median Tanner had higher bone acqusition rates than the placebo group with above-median Tanner scores. Relative to the placebo group, the supplemented group had increased yearly gains of bone content, area and density which represented about 1.5% of adult female values. Such increases, if held toadult skeletal maturity, could provide protection against future risk of osteoporotic fractures.

The role of vitamin D in the pathogenesis and treatment of osteoporosis

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It is well recognized that patients with postmenopausal osteoporosis usually exhibit some degree of calcium malabsorption and commonly have low serum concentrations of 1,25-dihydroxyvitamin D (calcitriol). Administration of calcitriol has been shown to normalize calcium absorption in patients with osteoporosis and, over the long term may have a stimulating effect on bone formation. Clinical trials have shown a significant reduction in osteoporotic fractures among calcitriol-treated patients. Hypercalcemia and hypercalciuria are infrequent complications of calcitriol therapy with physiologic doses (0.25 microg twice daily), and are most commonly related to excessive calcium intake (i.e., > 1000 mg daily).

Nutritional and biochemical studies on vitamin D and its active derivatives

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Yakugaku Zasshi (Japan), 1996, 116/6 (457-472)

We have performed nutritional and biochemical studies on vitamin D and its active derivatives and the following results are obtained. 1. Since recent studies have revealed that dietary supplement of vitamin D (D2 and D3) and calcium is effective for preventing osteoporosis, a simplified routine method for determination of vitamin D in foods is established and applied to the assay on the contents of vitamin D in various kinds of Japanese foods. 2. A simplified routine method for simultaneous determination of vitamin D and its metabolites in the plasma and milk is established and applied to nutritional and clinical studies. 3. Physiological activities of two kinds of novel vitamin D3 derivatives, 22-oxa-1alpha,25-dihydroxyvitamin D3 (22-oxa-1,25(OH)2D3, OCT) and 2beta-(3-hydroxypropoxy)-1,25(OH)2D3 (ED- 71) have been studied. OCT, which has less calcemic and stronger cell differentiation activities than 1,25(OH)2D3, is a candidate for curing leukemia and other cancers without hypercalcemia. We have clarified that the property is due to its weak binding affinity for vitamin D binding protein and rapid turn-over in the body and rapid excretion into bile. On the other hand, ED-71, which has stronger effects on intestinal calcium absorption and longer bone turn-over than 1,25(OH)2D3, is a candidate for curing osteoporosis. We have clarified that the properties are due to stronger binding affinity for DBP and longer half-life than 1,25(OH)2D3.

Osteoporosis and calcium ingest

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Bone mineral content related to calcium ingest is analyzed in 200 women through a case-control design. 75 were diagnosed of osteoporosis and the remaining 125 had normal bone mineral content. The age ranged between 48 and 55 years old, with climateric period lower than 18 months. Bone mass determination was carried out with double fotonic absortion densitomerty. The calcium ingest study was fulfilled through 24 hours before remind, with personal interview. It was repeated 4 times in a one year period. There were significant differences and also a positive correlation in bone mass related to calcium ingest even in trabecular or cortical bone.

Lower serum 25-hydroxyvitamin D is associated with increased bone resorption markers and lower bone density at the proximal femur in normal females: A population-based study

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Subclinical vitamin D deficiency is considered to be a risk factor for osteoporosis. Therefore, we studied vitamin D status and bone mineral density (BMD) in an age- and sex-stratified population based sample (209 males and 206 females aged between 50 and 80 years). In addition, urinary excretion of pyridinium crosslinks of collagen was determined in order to monitor bone resorption. We found a seasonal variation of serum 25-hydroxyvitamin D (25(OH)D) levels with higher values detected in the summer (27 +/- 10 ng/ml) and lower values measured in the winter (17 +/- 9 ng/ml). Further analyses were performed separately for winter and summer, respectively. We also excluded subjects taking osteotropic medication. In men, we found no significant relationship between vitamin D status and bone density or pyridinium crosslinks. In women, we found significant positive correlations between 25(OH)D and proximal femur BMD in winter ($r = 0.21$, $p < 0.05$) and in summer ($r = 0.36$, $p < 0.01$). The association between 25(OH)D and proximal femur BMD persisted after correction for age and body mass index. Serum 25(OH)D and urinary pyridinium crosslinks were inversely correlated in females in winter ($r = -0.24$, $p < 0.02$) and in summer ($r = -0.32$, $p < 0.02$). Our data support the hypothesis that already moderately low serum levels of 25(OH)D within the 'normal' range lead to osteopenia via increased bone resorption.

Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: A 3 year followup

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Objective. To determine the efficacy and safety of vitamin D 50,000 units/week and calcium 1,000 mg/day in the prevention of corticosteroid induced osteoporosis.

Methods. A minimized double blind, placebo controlled trial in corticosteroid treated subjects in a tertiary care university affiliated hospital. The sample was 62 subjects with polymyalgia rheumatica, temporal arteritis, asthma, vasculitis, or systemic lupus erythematosus. The primary outcome measure was the percentage change in bone mineral density (BMD) of the lumbar spine in the 2 treatment groups from baseline to 36 mo followup.

Results. BMD of the lumbar spine in the vitamin D and calcium treated group decreased by a mean (SD) of 2.6% (4.1%) at 12 mo, 3.7% (4.5%) at 24 mo, and 2.2% (5.8%) at 36 mo. In the placebo group there was a decrease of 4.1% (4.1%) at 12 mo, 3.8% (5.6%) at 24 mo, and 1.5% (8.8%) at 36 mo. The observed

differences between groups were not statistically significant. The difference at 36 mo was -0.693% (95% CI -5.34, 3.95).

Conclusion. Vitamin D and calcium may help prevent the early loss of bone seen in the lumbar spine as measured by densitometry of the lumbar spine. Longterm vitamin D and calcium in those undergoing extended therapy with corticosteroids does not appear to be beneficial.

Influence of life style in the MEDOS study

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MEDOS is a case-control study where 9,000 persons were interviewed with an extensive questionnaire, either at time of fracture or in age-matched controls. Both men and ium intake in the diet, urinary excretion of calcium, serum calcium, serum phosphate, serum parathormone and calcitonin. In children (10-14 years) with lactase deficiency and osteoporosis the mean value of calcium intake was smaller (540-670 mg per day) than in patients of the lactase-normal group (on average 820 mg per day). In children osteoporosis has developed 2-10 years after the hypolactasia diagnosis. In the group of postmenopausal women (50-60 years) calcium intake was smaller in the lactase-deficient group with osteoporosis (average 630 mg per day), in the lactase-normal group in postmenopausal women calcium intake was normal (about 1200 mg per day). Urinary excretion of calcium (per 24 h) and other laboratory analyses did not differ in patients with hypolactasia from patients of the lactase-normal group. Lactase deficiency appears to be one of several factors that predispose the development of osteoporosis, probably through diminished calcium intake.

Roles of diet and physical activity in the prevention of osteoporosis

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In recent years, much attention has been directed toward the prevention of osteoporosis, since this disease has become a leading cause of morbidity and mortality in elderly women. Research has demonstrated that the prevention of osteoporosis and osteoporosis-related fractures may best be achieved by initiating sound health behaviors early in life and continuing them throughout life. Evidence

suggests that osteoporosis is easier to prevent than to treat. In fact, healthy early life practices, including the adequate consumption of most nutrients, regular physical activity, and other healthy behaviors, contribute to greater bone mineral measurements and optimal peak bone mass by the fourth decade of life of females, and, perhaps, also of males. Several reports have shown that the adequate consumption of nutrients, calcium in particular, during the pre-pubertal and early post-pubertal years of females contribute to increased peak bone mass. Indeed, skeletal benefits from long-term calcium supplementation have been reported for females at practically every period of the life cycle. Vitamin D, which may be either consumed or produced endogenously through the action of sunlight, promotes calcium absorption and thereby enhances bone mineralization. Thus, the adequate consumption of calcium, in conjunction with vitamin D, in early life will likely optimize peak bone mass, and adequate intakes of these two nutrients should continue through the remainder of life to help maintain bone mass. On the other hand, excess phosphorus consumption may deter bone mineral accrual because of the resultant elevation of serum parathyroid hormone levels. Additionally, high intakes of protein, sodium, and caffeine may decrease bone mineral mass through increased urinary excretion of calcium. Vitamin K may also have an important positive effect on the development and maintenance of bone through its role in promoting carboxylations of the matrix protein, osteocalcin. In conclusion, the prevention of osteoporosis needs to begin during the pre-ubertal years and it should be continued throughout life. Bone mass can better be maintained later in life through adequate consumption of several nutrients with specific roles in calcium and bone metabolism, regular physical activity, and the practice of a healthy lifestyle. Mechanisms through which the nutrients and exercise affect bone mass will be explored.

Vitamin D in the treatment of osteoporosis revisited

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Interest in vitamin D treatment for osteoporosis has recently been revived because of the focus in various parts of the world on the elderly population, which is predominantly vitamin D deficient, in addition to postmenopausal osteoporosis due to estrogen withdrawal, which has been the central theme of osteoporosis research for many years. Combined use of other agents along with vitamin D has fortified the therapeutic armory against osteoporosis. The recent suggestion of a role of vitamin D receptor polymorphism in the development and progress of osteoporosis, possibly by interfering with its expected action, provoked intense discussions on the role of vitamin D in the pathogenesis and treatment of osteoporosis. Vitamin D receptor polymorphism may explain some of the racial differences in the incidence of osteoporosis and its complications. Responses to vitamin D treatment may also be predicted by vitamin D receptor allelic analysis, though the currently proposed allelic patterns are yet far from being widely

accepted. The outlook for vitamin D treatment for osteoporosis may require insight into vitamin D receptor, not only for vitamin D's given form, but also for a possible future form designed to intervene at the genomic level.

Prevention of bone loss in cardiac transplant recipients: A comparison of biphosphonates and vitamin D

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Transplantation (USA), 1996, 61/10 (1495-1499)

Bone mineral density is already abnormally reduced at the moment of cardiac transplantation and bone loss occurs at an impressive rate in the first postoperative year. The aim of the study was to compare two prophylactic medical regimens as to their efficacy in mitigating hone loss after transplantation. Forty-eight consecutive recipients were randomized to receive either alternating calcium carbonate and disodium etidronate (group A) or a daily supplement of calcium carbonate and alphacalcidol (group B). Bone mineral density measurements were performed immediately before hospital discharge and 6, 12, and 24 months after surgery using dual energy X-ray absorptiometry. Clinical events were recorded and roentgenograms of the spine were performed postoperatively and 1 and 2 years later. In both treatment groups bone loss remained significant at the level of the lumbar spine in the first postoperative year ($P<0.005$) and at the level of the femoral neck in the first ($P<0.005$) and the second ($P<0.05$) year after transplantation. Six months after transplantation, however, patients receiving alphacalcidol had a significant reduction in bone loss at the level of the lumbar spine ($P=0.047$) and at the level of the femoral neck ($P=0.043$). At the level of the femoral neck this decrease in bone loss was even more pronounced in the second postoperative year ($P<0.001$). In the group of patients treated with disodium etidronate, 4 recipients needed additional hospitalizations for treatment of symptomatic fractures at the level of the lumbar spine or the femoral neck. No such events happened in recipients receiving vitamin D supplements. Prophylactic administration of calcium carbonate and alphacalcidol after cardiac transplantation reduces bone loss and seems to decrease osteoporotic complications.

Prophylaxis of osteoporosis with calcium, estrogens and/or eelcatonin: Comparative longitudinal study of bone mass

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Maturitas (Ireland), 1996, 23/3 (327-332)

Objective: To evaluate three different therapeutic regimens for the prevention of osteoporosis in natural and surgical postmenopausal women who had been found to have rapid bone loss in analytical studies.

Methods: A total of 104 naturally or surgically postmenopausal women were studied, and subsequently followed-up during 1 year for avoidance of the influence of seasonal variation on bone mass, a factor overlooked in several studies. They were randomized into four groups of 26 patients each: the untreated control group (mean age 50 + or - 5 years); the hormonal replacement treatment (HRT) group (mean age 48 plus or minus 6 years), which was treated for 24 days each month with transdermal 17beta-estradiol, 50 mg/day, together with medroxiprogesterone, 10 mg during 12 days; the calcium group (mean age 50 + or - 4 years), which was treated with elemental calcium, 1 g/day; and the calcitonin group (mean age 50 plus or minus 5 years), which was treated for 10 days each month with eel calcitonin, 40 IU/day and with elemental calcium, 500 mg/day. Full-body bone densitometry, for measuring total body bone mineral content (TBBMC), was carried out in all the women at baseline and 1 year. TBBMC was corrected for body weight by dividing its value by body weight (TBBMC/W).

Results: After 1 year TBBMC/W was lower in every group: -2.14% ($P < 0.001$) in the control group; -0.14% (P = NS) in the HRT group ($P < 0.05$ vs. controls); -0.18% (P = NS) in the calcium group ($P < 0.05$ vs. controls); and -0.06% (P = NS) in the calcitonin group ($P < 0.01$ vs. controls; $P < 0.05$ vs. calcium and HRT).

Conclusions: These findings show that all three treatments are effective in the prevention of postmenopausal loss of bone mass.

Open-label, controlled study on the metabolic and absorptiometric effects of calcitriol in involutional osteoporosis

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Calcitriol 0.5 microg twice daily, in combination with a low dietary calcium intake, was administered for 2 years to 35 women (mean age 64.6 + or - 8.3 years) with involutional osteoporosis; 45 women (mean age 63.5 + or - 8.7 years) with osteoporosis ingested dietary calcium 1000 mg/day and were considered a control group. Total body bone mineral density (BMD) and BMD of major anatomical areas were measured (Lunar DPX). In the calcitriol group, significant increases in serum and urinary calcium levels were observed after 12 and 24 months; urinary hydroxyproline excretion did not change significantly. No differences in blood urea nitrogen or serum creatinine were observed during calcitriol therapy, and none of the patients experienced symptomatic renal lithiasis. Increases in total body, spine and leg BMD were observed after 12 and 24 months of calcitriol therapy (+0.63%, +1.15% and +0.56%, and +0.85%, +1.37% and +0.35%,

respectively). In the control group, total body BMD and BMD of the spine, trunk, arms and legs decreased significantly. The mean percentage BMD differences between the 2 study groups were statistically significant. In the control group, spinal height declined progressively and significantly from baseline (-1.61% and -3.02% after 12 and 24 months, respectively), while in calcitriol-treated patients the decrease was less marked (-1.11% and -1.15%, respectively): the difference between the 2 groups was statistically significant ($p < 0.01$) after 24 months. In conclusion, calcitriol 1 microg/day plus a low dietary calcium intake may be considered safe and effective in patients with involutional osteoporosis.

Nutritional prevention of aging osteoporosis

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Aging is accompanied by a decrease in bone mass, with the risk of developing osteoporosis, of which the consequence is atraumatic fractures. These fractures, particularly those of the proximal femur, are associated with an important socioeconomic impact.Calcium supplements contribute to prevent bone loss in the elderly. On the other hand, protein repletion administered to compensate highly frequent malnutrition in the elderly can decrease medical complications following a fracture of the proximal femur, and exerts a favorable influence on bone mineral density.

Effects of 2 years' treatment of osteoporosis with 1alpha-hydroxy vitamin D3 on bone mineral density and incidence of fracture: A placebo-controlled, double-blind prospective study

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A two-year double-blind study monitored and evaluated the effects of 1alpha-hydroxy vitamin D3 (1alpha(OH)D3) on the lumbar (L2-4BMD) and total body bone mineral densities (TBBMD) and occurrence of fracture in 113 female osteoporotic patients receiving 0.75 microg/day of 1alpha(OH)D3 (n=57) or a placebo (n=56) with calcium supplementation in both groups. L2-4BMD increased 1.81% and 2.32% after one and 2 years in the 1alpha(OH)D3 group, but decreased 1.89% ($P<0.05$) and 0.28% in the placebo group. A significant difference ($P<0.01$) existed between the two groups after one year. TBBMD decreased significantly in the placebo group by 3.34% ($P<0.01$) and 3.52% after one and 2 years. Six new fractures occurred in the control group, but only two in the 1alpha(OH)D3 group (Odd's ratio=0.343, 95% confidence range; 0.0648-

1.815). There were no serious adverse effects of the 1alpha(OH)D3 treatment. It was concluded that two-year treatment with 1alpha(OH)D3 increased the lumbar BMD and inhibited the decrease in TBBMD. Although it was not significant, new fracture occurrence in the 1alpha(OH)D3 group was around 1/3 of that in the control group.

Energy and nutrient intake in patients with CF

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Background: Nutritional assessment and management remain important issues in the treatment of CF patients despite newer developments as lung transplantation, inhalation with DNase and gene therapy.

Methods: The nutritional status of 26 patients (mean age 15,8 years; 16 male; 46% homozygous, 38% heterozygous for DeltaF 508, remaining unknown; 3 pancreas sufficient, Shwachman score intermediate to excellent) of our CF clinic was analyzed using a three days protocol, the precise weighing method and comparison of data with the official dietary recommendations.

Results: The average energy intake was below the 130% officially recommended and the fat intake was below the aimed 40% of total energy intake. The regression analysis revealed positive correlations between energy intake and SDS(Height) and Shwachman score and SDS(Weight) respectively. Food contained an insufficient amount of unsaturated fatty acids. Water soluble vitamins were supplemented adequately besides folic acid, but intake of fat soluble vitamins E and A often was insufficient despite extra Vitamin-Capsules. Every second patient did not take enough minerals as calcium, magnesium or iron.

Conclusions: This analysis underlines how important the regular assessment of the nutritional status can be for the individual nutritional management of CF patients even if clinical symptoms of deficiencies could not be detected. An increase of fat intake as a main source of energy, essential fatty acids and fat soluble vitamins has to be encouraged as well as the increased use of milk and milk products for the prevention of osteoporosis. Iron and folic acid are further critical nutrients.

1,25-Dihydroxyvitamin D3 enhances the enzymatic activity and expression of the messenger ribonucleic acid for aromatase cytochrome P450 synergistically with dexamethasone depending on the vitamin D receptor level in cultured human osteoblasts

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Endocrinology (USA), 1996, 137/5 (1860-1869)

Not every postmenopausal woman with a low level of estrogen suffers from osteoporosis, and no correlation of bone density with serum estrogen level, but a significant correlation with adrenal androgens, is often noted. Vitamin D3 has been reported to be osteoclastic in vitro, whereas the effectiveness of vitamin D3 for the treatment of osteoporosis is clinically relevant. To study the roles of these factors in the development of osteoporosis, we characterized aromatase activity converting androgens to estrogens in human osteoblasts, because postmenopausal women maintain considerable levels of adrenal androgens. Glucocorticoids at 10-9-10-7 M transiently induced the expression and enzymatic activity of aromatase cytochrome P450 (P450(AROM)) in primary cultured osteoblasts, and the K(m) value for androstenedione (4.7 + or -2.9 nM) was lower than that in adipose tissue and skin. Human osteoblasts showed a promoter specificity different from that found in other tissues. 1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3) alone did not induce aromatase activity, but enhanced and maintained glucocorticoid-induced P450(AROM) gene expression. This synergistic effect was not observed by other sex steroids or retinoic acids. The enhancement of P450(AROM) activity by 1,25(OH)2D3 varied from 0.94-fold (no enhancement) to 2.40-fold (maximal enhancement) among the individual human osteoblasts examined, but the magnitude of the enhancement was significantly correlated with the level of vitamin D receptor messenger RNA ($P < 0.05$). Cycloheximide did not abolish the synergistic effect of 1,25(OH)2D3, suggesting that de hove protein synthesis is not required for the synergism with 1,25-(OH)2D3. These results suggest that bone tissue can synthesize estrogen from adrenal androgens by a unique aromatase activity depending on the level of vitamin D receptor expressed.

Effects of hormonal therapies and dietary soy phytoestrogens on vaginal cytology in surgically postmenopausal macaques

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Fertility and Sterility (USA), 1996, 65/5 (1031-1035)

Objective: To evaluate the effects of conjugated equine estrogens, medroxyprogesterone acetate (MPA), conjugated equine estrogens combined with MPA, tamoxifen, and soybean estrogens on vaginal cytology in surgically postmenopausal cynomolgus macaques (Macaca fascicularis).

Design: Randomized long-term experimental trial.

Setting: Cytologic samples were taken from animals in two long-term randomized studies of the effects of hormonal and dietary effects on atherosclerosis.

Patients: Surgically postmenopausal cynomolgus macaques.

Interventions: Conjugated equine estrogens, MPA, conjugated equine estrogens combined with MPA, tamoxifen, and soybean estrogens were given via the diet, at doses scaled from those given to women.

Main Outcome Measure: Vaginal cytologic maturation index.

Results: Conjugated equine estrogens elicited a marked maturation effect, which was antagonized partially by the addition of MPA. Tamoxifen produced a lesser estrogenic response. The cytologic pattern in animals given soybean estrogens or MPA alone did not differ from that of controls.

Conclusion: Soybean estrogens at the doses given do not exert an estrogenic effect on the vagina of macaques. Conjugated equine estrogens are potent inducers of vaginal keratinization in this model; tamoxifen has a lesser effect. Medroxyprogesterone acetate partially antagonizes the effects of conjugated equine estrogens, and has no effect when given alone. The results support the possibility that soybean estrogens may be a 'tissue-selective' estrogen with minimal effects on the reproductive tract.

Evaluation of acceptability, tolerance and observance of a new calcium-vitamine D combination

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Rhumatologie (France), 1996, 48/2 (37-42)

The aim of this trial was to assess in 190 patients randomized in two identical groups the tolerance and acceptability of a new calcium-vitamin D combination, OROCAL (R) Vitamine D3 (chewable tablets containing calcium 500 mg and vitamine D3 400 IU) in order to compare it with the same doses of calcium (1 g/day) and vitamin D (800 IU/day), obtained by taking two SANDOCAL (R) 500 mg bags and two STEROGYL (R) drops/day. After 10 weeks, patients were asked about the acceptability of the treatments and the occurrence of adverse effects. They had also to answer before and after treatment a guestionnaire listing 10 gastrointestinal symptoms. The observance and the acceptability have been better under OROCAL (R) Vitamine D3, with drop out 3 times less numerous under this combination than under the SANDOCAL (R) + STEROGYL (R) solution. The number of patients with a gastrointestinal symptom and the total number of these symptoms were statistically higher in the SANDOCAL (R) + STEROGYL (R) group, this association being more frequently responsible for flatulences, probably because the solution is effervescent.

Effects of vitamin K on bone mass and bone metabolism

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Journal of Nutrition (USA), 1996, 126/4 SUPPL. (1187S-1191S)

Vitamin K is involved in blood coagulation and in bone metabolism via the carboxylation of glutamate residues in (hepatic) blood coagulation factors and (osteoblastic) bone proteins. The bioavailability of nutritional vitamin K depends on the type of food, the dietary fat content, the length of the aliphatic side chain in the K-vitamer and probably also the genetically determined polymorphism of apolipoprotein E. Although undercarboxylation of blood coagulation factors is very rare, undercarboxylated osteocalcin (bone Gla-protein) is frequently found in postmenopausal women. Supplementation of these women with extra vitamin K causes the markers for bone formation to increase. In parallel, a decrease of the markers for bone resorption is frequently seen. Insufficient data are available to conclude that the regular administration of vitamin K concentrates will reduce the loss of bone mass in white women at risk for developing postmenopausal osteoporosis.

Calcium and vitamin D nutritional needs of elderly women

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Journal of Nutrition (USA), 1996, 126/4 Suppl. (1165S-1167S)

Because osteoporosis is irreversible, the most effective approach to reduce morbidity and mortality from this disease is to maximize peak bone mass and minimize bone loss. This presentation reviews the evidence that calcium and vitamin D influence rates of bone loss in postmenopausal women. In the first five or more years after menopause, women lose bone very rapidly. During this period, high dose calcium supplementation modestly reduces cortical loss from long bones but has minimal effect on more trabecular sites such as the spine. In addition, vitamin D appears to enhance the effectiveness of supplemental calcium. Late postmenopausal women are generally more responsive to added calcium, and those with the lowest dietary calcium intakes benefit the most. In calcium-replete women, supplementation with vitamin D reduces bone loss and fracture incidence. Available evidence indicates that postmenopausal women should consume 1000-1500 mg of calcium and 400 to 800 IU of vitamin D per day to minimize bone loss.

Vitamin D and bone health

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Journal of Nutrition (USA), 1996, 126/4 Suppl. (1159S-1164S)

Vitamin D plays an essential role in maintaining a healthy mineralized skeleton for most land vertebrates including humans. Sunlight causes the photoproduction of vitamin D3 in the skin. Once formed, vitamin D3 is metabolized sequentially in the liver and kidney to 1,25-dihydroxy vitamin D. The major biological function of 1,25-dihydroxyvitamin D is to keep the serum calcium and phosphorus concentrations within the normal range to maintain essential cellular functions and to promote mineralization of the skeleton. Most foods do not contain any vitamin D. Foods fortified with vitamin D have a variable amount present and cannot be depended on as a sole source of vitamin D nutrition. Exposure to sunlight provides most humans with their vitamin D requirement. Aging, sunscreen use and the change in the zenith angle of the sun can dramatically affect the cutaneous production of vitamin D3. Vitamin D insufficiency and vitamin D deficiency is now being recognized as a major cause of metabolic bone disease in the elderly. Vitamin D deficiency not only causes osteomalacia but can exacerbate osteoporosis. It is generally accepted that an increase in calcium intake to 1000-1500 mg/d along with an adequate source of vitamin D of at least 400 IU/d is important for maintaining good bone health.

Heated oyster shell-seaweed calcium (AAA Ca) on osteoporosis

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Calcified Tissue International (USA), 1996, 58/4 (226-230)

A randomized, prospective, double-blind lest was curried out to compare the effects of heated oyster shell-seaweed calcium (AAA Ca), calcium carbonate, and placebo in 58 elderly, hospitalized women with the mean age of 80 divided into three groups. Group A received 900 mg/day Ca as AAA Ca. Group B 900 mg/day Ca as CaCO3, and Group C placebo besides regular hospital diet containing approximately 600 mg Ca/day for 24 months. From the 25th to the 30th month, all groups were given AAA Ca. Lumbar spine and radial bone mineral density (BMD) were measured at 3-month intervals. Urinary Ca/Cr and serum alkaline phosphatase, intact and midportion serum parathyroid hormone (PTH), and calcitonin were also measured at intervals. From the 6th to the 24th month of the study, the ratio of lumbar spine BMD (L2-L4 by DPX, Lunar) to the basal pretest value was consistently mid significantly higher in Group A than Group C but not higher in Group B than in Group C. PTH, measured 12 months after the beginning of the study, was lower in Group A than in Group C, but no significant difference

was found between Groups B and C. At 3 months after the placebo was switched to AAA Ca in Group C. serum PTH was significantly decreased from the level during placebo supplement. Morning urine Ca/Cr decreased in Groups A after 18 months and in B after 12 months, but not in C. Serum alkaline phosphatase decreased in Group A significantly compared with Group C, but not in Group B. AAA Ca appears to be effective for increasing BMD in elderly subjects.

The lack of influence of long-term potassium citrate and calcium citrate treatment in total body aluminum burden in patients with functioning kidneys

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Journal of the American College of Nutrition (USA), 1996, 15/1 (102-106)

Background: It has been suggested that citrate salts might enhance aluminum (Al) absorption from a normal diet, posing a threat of Al toxicity even in subjects with normal renal function. We have recently reported that in normal subjects and patients with moderate renal failure, short-term treatment with tricalcium dicitrate (Ca,Cit2) does not significantly change urinary and serum Al levels. However, we have not assessed total body Al stores in patients on long-term citrate treatment.

Objective: The objective of this study was to ascertain body content of Al non-invasively using the increment in serum and urinary Al following the intravenous administration of deferoxamine (DFO) in patients with kidney stones and osteoporotic women undergoing long-term treatment with potassium citrate (K3Cit) or Ca3Cit2, respectively.

Methods: Ten patients with calcium nephrolithiasis and five with osteoporosis who were maintained on potassium citrate (40 mEq/day or more) or calcium citrate 800 mg calcium/day (40 mEq citrate) for 2 to 8 years, respectively, and 1 h normal volunteers without a history of regular aluminum-containing antacid use participated in the study. All participants completed the 8 days of study, during which they were maintained on their regular home diet. Urinary Al excretion was measured during a two-day baseline before (Days 5, 6) and for 1 day (Day 7) immediately following a single intravenous dose of DFO (40 mg/kg). Blood for Al was obtained before DFO administration, and at 2, 5 and 24 hours following the start of the infusion.

Results: The median 24-hour urinary Al excretion (microg/day) at baseline versus post-DFO value was 15.9 vs. 44.4 in the normal subjects and 13.3 vs. 35.7 in the patients. These values were all within normal limits and did not change significantly following DFO infusion ($p = 0.003$ and $p = 0.0001$, respectively). The median change of 17.1 microg/day in urinary Al in the normal subjects was not significantly different from the 18.7 microg/day change measured in the patient group (p 0.30). Similarly, no change in the mean serum Al was detected at

any time following the DFO infusion, either in the patient or control group (patients 4.1 to 4.3 ng/ml, controls 7.4 to 4.6 ng/ml).

Conclusion: The results suggest that abnormal total body retention of Al does not occur during long term citrate treatment in patients with functioning kidneys.

Dietary soybean protein prevents bone loss in an ovariectomized rat model of osteoporosis

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Journal of Nutrition (USA), 1996, 126/1 (161-167)

The purpose of this study was to examine whether soybean protein isolate prevents bone loss induced by ovarian hormone deficiency. Thirty-two 95-d- old Sprague-Dawley rats were randomly assigned to four treatment groups (sham-operated (sham); ovariectomized (ovx); ovx + soybean; ovx + 17beta- estradiol (E2)) and killed after 30 d. Rats in the sham, ovx and ovx + 17beta- estradiol groups were fed a casein-based diet, and the soybean group was fed soybean protein isolate instead of casein; the diets were otherwise comparable. Rats in the ovx group had significantly lower densities of the right femur ($P < 0.001$) and the fourth lumbar vertebra ($P < 0.05$) than rats in the sham group. These lower bone densities were not observed in animals receiving 17beta-estradiol or fed soybean. The ovx group also had significantly ($P < 0.01$) greater serum concentrations of 1,25-dihydroxycholecalciferol than the other three groups. Our findings suggest that dietary soybean protein is effective in preventing bone loss due to ovarian hormone deficiency. Because serum activities of both alkaline phosphatase and tartrate-resistant acid phosphatase were significantly greater in the ovx group and in the ovx + soybean group but not in the group receiving 17beta-estradiol, compared with sham animals, this confirms that ovariectomy enhances and 17beta-estradiol suppresses the rate of bone turnover. Despite the higher rate of bone turnover in the soybean-fed animals, the vertebral and femoral bone densities of these rats were significantly greater than those of rats in the ovx group, suggesting that formation exceeded resorption. Further studies are needed to clarify whether this protective effect on bone is due to the protein itself or to the presence of isoflavones in soybean protein.

Bone mineral density in mother-daughter pairs: Relations to lifetime exercise, lifetime milk consumption, and calcium supplements

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American Journal of Clinical Nutrition (USA), 1996, 63/1 (72-79)

This study investigated associations between lifetime milk consumption, calcium intake from supplements, lifetime weight bearing exercise, and bone mineral density (BMD) among 25 elderly women (mean age 72 y) and their premenopausal daughters (mean age 41 y).The BMD of the total, axial, and peripheral skeleton was measured by dual energy X-ray absorptiometry. Lifetime milk consumption, supplemental calcium intake, and weight-bearing exercise were estimated retrospectively by questionnaire and interview. In multiple linear-regression analyses, mothers' total and peripheral BMD were positively associated with supplemental calcium intake after age 60 y, body weight, current estrogen replacement therapy (ERT), and past oral contraceptive (OC) use, and negatively associated with age and height (all $P < 0.05$). Mothers' axial BMD was positively correlated with body weight and past OC use. Among daughters, lifetime weight-bearing exercise was a predictor of total and peripheral BMD, whereas total lean mass was a predictor of axial BMD. Mothers' lifetime milk consumption was positively associated with that of their daughters. Mothers' and daughters' peripheral BMD values were positively correlated after adjustment for daughters' exercise, and mothers' age, body weight, and ERT. These results suggest that calcium supplementation and exogenous estrogen positively influence bone mass in postmenopausal years. Our findings lend support to recommendations for physical activity as a means of osteoporosis prevention. In the age groups studied, the effects of behavioral and hormonal factors on BMD appeared to dominate over familial similarity, which suggests thai women may successfully enhance their genetically determined bone mass through weight-bearing exercise, post menopausal ERT, and adequate calcium intake.

Whey protein stimulated the proliferation and differentiation of osteoblastic MC3T3-E1 cells.

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Nutritional Science Laboratory, Snow Brand Milk Product Co. Ltd., Saitama, Japan.
Biochem Biophys Res Commun 1996 Jun 14;223(2):445-9

We examined the effects of whey protein on osteoblastic MC3T3-E1 cells. This protein caused dose-dependent increases in [3H]thymidine incorporation and DNA content in the cells. It also increased the total protein and hydroxyproline contents in the cells. These activities were heat resistant when the protein was heated at 75 degrees C to 90 degrees C for 10 min. Heat-treated whey protein was first fractionated on a Mono S column, and the active fraction (basic protein fraction) was then applied to Superose 12. The molecular weights of the active components were approximately 10,000 and 14,000 Da, as determined with gel filtration. The inner solution of an everted gut-sac incubated in a solution of intact BP (basic protein), pepsin-digested BP or pepsin/pancreatin-digested BP also stimulated the [3H]thymidine incorporation. Thus these active components can possibly permeate or be absorbed by the intestines. We propose the possibility that the active component in the whey protein plays an important role in bone formation by activating osteoblasts.

23. Parkinson's Disease

Preventative and curative options include:

L-tyrosine, NADH, acetyl-L-carnitine, niacinamide, ginkgo biloba, ginseng, licorice root, royal jelly, freeze-dried liver, MSM, calcium, phosphatidylserine, co-enzyme Q10, vitamin C, vitamin E, grape seed extract, gamma tocopherol, magnesium, tryptophan, lecithin, melatonin, DHEA, pregnenolone, bee pollen, chlorella, spirulina, probiotic.

Protective effect of melatonin in a chronic experimental model of Parkinson's disease.

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Brain Res. 2002 Jul 12;943(2):163-73.

Parkinson's disease is a chronic condition characterized by cell death of dopaminergic neurons mainly in the substantia nigra. Among the several experimental models used in mice for the study of Parkinson's disease 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced parkinsonism is perhaps the most commonly used. This neurotoxin has classically been applied acutely or sub-acutely to animals. In this paper we use a chronic experimental model for the study of Parkinson's disease where a low dose (15 mg/kg bw) of MPTP was administered during 35 days to mice to induce nigral cell death in a non-acute way thus emulating the chronic condition of the disease in humans. Free radical damage has been implicated in the origin of this degeneration. We found that the antioxidant melatonin (500 microg/kg bw) prevents cell death as well as the damage induced by chronic administration of MPTP measured as number of nigral cells, tyrosine hydroxylase levels, and several ultra-structural features. Melatonin, which easily passes the blood-brain barrier and lacks of any relevant side-effect, is proposed as a potential therapy agent to prevent the disease and/or its progression.

The effect of dehydroepiandrosterone sulfate administration to patients with multi-infarct dementia.

Azuma T, Nagai Y, Saito T, Funauchi M, Matsubara T, Sakoda S. The Second Department of Internal Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.

J Neurol Sci. 1999 Jan 1;162(1):69-73

We measured cerebrospinal fluid (CSF) levels of dehydroepiandrosterone sulfate (DHEAS) by radioimmunoassay in seven patients with multi-infarct dementia (MID), fourteen age- and gender-matched non-demented patients with a history of cerebral infarction and fifteen age- and gender-matched patients without neurological disorders. The levels of DHEAS in CSF of patients with MID were significantly lower than those in non-demented patients with a history of cerebral infarction or those in patients without neurological disorders. Daily intravenous administration of 200 mg DHEAS for 4 weeks markedly increased serum and CSF levels of DHEAS in seven MID patients, improved decrease of daily activities and emotional disturbances in three patients and EEG abnormalities in two patients. The DHEAS therapy may provide a beneficial effect on MID patients.

Mitochondria, NO and neurodegeneration.

Beal MF. Neurochemistry Laboratory, Neurology Service/WRN 408, Massachusetts General Hospital, Boston, USA.

Biochem Soc Symp. 1999;66:43-54.

A role for mitochondrial dysfunction in neurodegenerative disease is gaining increasing support. Mitochondrial dysfunction may be linked to neurodegenerative diseases through a variety of different pathways, including free-radical generation, impaired calcium buffering and the mitochondrial permeability transition. This can lead to both apoptotic and necrotic cell death. Recent evidence has shown that there is a mitochondrial defect in Friedreich's ataxia, which leads to increased mitochondrial iron content, that appears to be linked to increased free-radical generation. There is evidence that the point mutations in superoxide dismutase which are associated with amyotrophic lateral sclerosis may contribute to mitochondrial dysfunction. There is also evidence for bioenergetic defects in Huntington's disease. Studies of cybrid cell lines have implicated mitochondrial defects in both Parkinson's disease and Alzheimer's disease. If mitochondrial dysfunction plays a role in neurodegenerative diseases then therapeutic strategies such as coenzyme Q10 and creatine may be useful in attempting to slow the disease process.

Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3,tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice.

Beal MF, Matthews RT, Tieleman A, Shults CW. Neurology Service, Massachusetts General Hospital, Boston, MA, USA.

Brain Res. 1998 Feb 2;783(1):109-14.

We investigated whether oral administration of coenzyme Q10 (CoQ10) could attenuate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in one-year-old mice. Four groups of one-year-old, male C57BL/6 mice received a either standard diet or a diet supplemented with CoQ10 (200 mg/kg/day) for five

weeks. After four weeks, one group that had received the standard diet and one group that had received the CoQ10 supplemented diet were treated with MPTP. The four groups continued on their assigned diets for an additional week prior to sacrifice. Striatal dopamine concentrations were reduced in both groups treated with MPTP, but they were significantly higher (37%) in the group treated with CoQ10 and MPTP than in the group treated with MPTP alone. The density of tyrosine hydroxylase immunoreactive (TH-IR) fibers in the caudal striatum was reduced in both MPTP-treated groups, but the density of TH-IR fibers was significantly (62%) greater in the group treated with CoQ10 and MPTP than in the group treated with MPTP alone. Our results indicate that CoQ10 can attenuate the MPTP-induced loss of striatal dopamine and dopaminergic axons in aged mice and suggest that CoQ10 may be useful in the treatment of Parkinson's disease.

Niacin depletion in Parkinsonian patients treated with L-dopa, benserazide and carbidopa.

Bender DA, Earl CJ, Lees AJ.

Clin Sci (Lond) 1979 Jan;56(1):89-93

1. Benserazide and carbidopa, decarboxylase inhibitors used in the treatment of Parkinson's disease, have been shown to inhibit the enzyme kynurenine hydrolase in rat and mouse liver. This results in reduced synthesis of nicotinamide coenzymes from tryptophan, and hence an increased reliance on dietary niacin. 2. Pellagra might be expected as a result of this inhibition of endogenous synthesis of nicotinamide nucleotides, but has not been reported in patients treated with either drug. 3. The urinary excretion of N1-methyl-nicotinamide, a product of nicotinamide nucleotide metabolism, is considerably reduced in patients treated with dopa alone or in combination with an inhibitor of peripheral dopa decarboxylase, to as low as 40% of the control value. This means that many of these patients could be classified as 'at risk' of niacin deficiency, even if not frankly deficient. 4. Patients treated with dopa plus a decarboxylase inhibitor, but not those treated with dopa alone, also show a reduced excretion of xanthurenic acid, and an increased excretion of kynurenine, as would be expected after inhibition of the kynurenine pathway, and possibly indicative of marginal vitamin B6 deficiency.

L-tryptophan: a rational anti-depressant and a natural hypnotic?

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Aust N Z J Psychiatry. 1988 Mar;22(1):83-97.

L-tryptophan is an essential amino acid which is the metabolic precursor of serotonin. Because of the evidence that serotonin deficiency may be an aetiological factor in some sorts of affective disorder and that serotonin is important in the biochemistry of sleep, L-tryptophan has been suggested as a "rational" anti-depressant and as a "natural" hypnotic. This paper reviews the

biochemistry and pharmacology of L-tryptophan as well as the literature of the clinical trials that have been conducted with it and suggests that, by itself, L-tryptophan may be useful in mild cases of depression accompanied by endogenous features and cases of bipolar disorder resistant to standard treatments. It also potentiates the monoamine oxidase inhibitors and possibly the serotonergic tricyclic drugs. L-tryptophan may improve the depressed mood of Parkinsonian patients and has a clinically useful hypnotic action. There is evidence it may be useful in organic mental disorders induced by levodopa. Dosage schedules, contraindications and complications are discussed.

Melatonin attenuates MPP+-induced neurodegeneration and glutathione impairment in the nigrostriatal dopaminergic pathway.

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J Pineal Res. 2002 May;32(4):262-9.

In this study we selected a rat model of Parkinson's disease (PD) by using intrastriatal infusion of the 1-methyl-4-phenyl-pyridinium ion (MPP+) to investigate the neuroprotective action of melatonin and its inhibitory activity on MPP+-impaired glutathione (GSH) system in the nigrostriatal system. Results show that MPP+ caused not only a severe neuronal injury in the striatum and in the ipsilateral substantia nigra (SN), but it also induced a significant decrease in GSH levels and an increase in the GSSG/GSH ratio 3 days after intrastriatal MPP+ infusion. Intraperitoneal co-administration of melatonin (10 mg/kg, five times) significantly attenuated MPP+-induced nigrostriatal neurotoxicity and GSH impairment. Depletion of cytosolic GSH by L-buthionine sulfoximine (BSO) did not cause neuronal damage by itself. It, however, when co-administrated with MPP+, potentiated the GSH reduction in the striatum, without aggravating nigrostriatal neurodegeneration induced by MPP+. Moreover, the MPP+-caused neuronal damage was positively correlated with a rising ratio of GSSG/GSH, but not with a drop of GSH. These results suggest that the MPP+-triggered oxidative stress may play a more important role than the loss of the antioxidant GSH in determining neuronal injury. Interestingly, the neuronal damage and oxidative stress elicited by co-treatment of BSO with MPP+ were effectively reduced by melatonin. Our results hence provide direct evidence showing that melatonin attenuates MPP+-induced nigrostriatal dopaminergic injury by its ability to impede the increase of GSSG/GSH ratio; therefore melatonin may have therapeutic implications in PD.

Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease.

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J Neurochem. 2002 Jan;80(1):101-10.

Although the cause of Parkinson's disease (PD) is unknown, data suggest roles for environmental factors that may sensitize dopaminergic neurons to age-related dysfunction and death. Based upon epidemiological data suggesting roles for dietary factors in PD and other age-related neurodegenerative disorders, we tested the hypothesis that dietary folate can modify vulnerability of dopaminergic neurons to dysfunction and death in a mouse model of PD. We report that dietary folate deficiency sensitizes mice to MPTP-induced PD-like pathology and motor dysfunction. Mice on a folate-deficient diet exhibit elevated levels of plasma homocysteine. When infused directly into either the substantia nigra or striatum, homocysteine exacerbates MPTP-induced dopamine depletion, neuronal degeneration and motor dysfunction. Homocysteine exacerbates oxidative stress, mitochondrial dysfunction and apoptosis in human dopaminergic cells exposed to the pesticide rotenone or the pro-oxidant Fe(2+). The adverse effects of homocysteine on dopaminergic cells is ameliorated by administration of the antioxidant uric acid and by an inhibitor of poly (ADP-ribose) polymerase. The ability of folate deficiency and elevated homocysteine levels to sensitize dopaminergic neurons to environmental toxins suggests a mechanism whereby dietary folate may influence risk for PD.

Oxidative stress and antioxidant therapy in Parkinson's disease.

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Prog Neurobiol. 1996 Jan;48(1):1-19.

Parkinson's disease, known also as striatal dopamine deficiency syndrome, is a degenerative disorder of the central nervous system characterized by akinesia, muscular rigidity, tremor at rest, and postural abnormalities. In early stages of parkinsonism, there appears to be a compensatory increase in the number of dopamine receptors to accommodate the initial loss of dopamine neurons. As the disease progresses, the number of dopamine receptors decreases, apparently due to the concomitant degeneration of dopamine target sites on striatal neurons. The loss of dopaminergic neurons in Parkinson's disease results in enhanced metabolism of dopamine, augmenting the formation of H2O2, thus leading to generation of highly neurotoxic hydroxyl radicals (OH.). The generation of free radicals can also be produced by 6-hydroxydopamine or MPTP which destroys striatal dopaminergic neurons causing parkinsonism in experimental animals as well as human beings. Studies of the substantia nigra after death in Parkinson's disease have suggested the presence of oxidative stress and depletion of reduced glutathione; a high level of total iron with reduced level of ferritin; and deficiency of mitochondrial complex I. New approaches designed to attenuate the effects of oxidative stress and to provide neuroprotection of striatal dopaminergic neurons in Parkinson's disease include blocking dopamine transporter by mazindol, blocking NMDA receptors by dizocilpine maleate, enhancing the survival of neurons by giving brain-derived neurotrophic factors, providing antioxidants such as vitamin E, or inhibiting monoamine oxidase B (MAO-B) by selegiline. Among all of these experimental therapeutic refinements, the use of selegiline has been most successful in that it has been shown that selegiline may have a neurotrophic

factor-like action rescuing striatal neurons and prolonging the survival of patients with Parkinson's disease.

An open trial of high-dosage antioxidants in early Parkinson's disease.

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Am J Clin Nutr 1991 Jan;53(1 Suppl):380S-382S

High dosages of tocopherol and ascorbate were administered to patients with early Parkinson's disease as a preliminary open-labeled trial for the eventual controlled double-blind study evaluating antioxidants as a test of the endogenous toxin hypothesis of the etiology of Parkinson's disease. The primary endpoint of the trial was the need to treat patients with levodopa. The time when levodopa became necessary in the treated patients was compared with another group of patients followed elsewhere and not taking antioxidants. The time when levodopa became necessary was extended by 2.5 y in the group taking antioxidants. The results of this pilot study suggest that the progression of Parkinson's disease may be slowed by the administration of these antioxidants. A large multicenter, controlled clinical trial currently underway in North America evaluating tocopherol and deprenyl has the potential to confirm these results.

A pilot trial of high-dose alpha-tocopherol and ascorbate in early Parkinson's disease.

Fahn S. Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY.

Ann Neurol 1992;32 Suppl:S128-32

High dosages of a combination of alpha-tocopherol and ascorbate were administered to patients with early Parkinson's disease as an open-labeled trial and pilot study to test the endogenous toxic hypothesis of the etiology of Parkinson's disease. Patients receiving concomitant amantadine and anticholinergics were allowed to participate, but those receiving levodopa or dopamine agonists were not. The study was begun prior to the availability of deprenyl. The primary end point of the trial was progression of the disease until patients needed treatment with levodopa or a dopamine agonist. The time when levodopa became necessary in the treated patients was compared to another group of patients followed elsewhere who did not receive antioxidants. The time when levodopa became necessary was extended by 2.5 years in the group receiving alpha-tocopherol and ascorbate. Results of this pilot study suggest that the progression of Parkinson's disease may be slowed by administration of these antioxidants. Controlled clinical trials using double-blind randomization techniques are required to confirm these results.

Normalization of brain serotonin by L-tryptophan in levodopa-treated rats.

Fahn S, Snider S, Prasad AL, Lane E, Makadon H.

Neurology. 1975 Sep;25(9):861-5.

To test possible biochemical mechanisms by which L-tryptophan may reverse mental side effects of levodopa therapy in parkinsonism we administered levodopa, 250 mg per kilogram intraperitoneally, alone and with L-tryptophan, 500 mg per kilogram intraperitoneally, to rats pretreated with the peripheral dopa decarboxylase inhibitor, carbidopa (25 mg per kilogram). Rats were decapitated 0.5, 1, and 2 hours following amino acid injection and brain levels of amino acids, amines, and acid metabolites were determined. As expected, levodopa alone reduced tryptophan and serotonin and increased dopa and dopamine at the 1 and 2 hour intervals. Concurrent administration of L-tryptophan did not significantly alter the increased dopa and dopamine but did restore serotonin levels to within normal range at all time points. If similar events occur in parkinsonian patients, normalization of brain serotonin and not competitive reduction of brain dopa and dopamine may be the basis for the improvement in mental status.

Frontal dysfunction in early Parkinson's disease.

Farina E, Cappa SF, Polimeni M, Magni E, Canesi M, Zecchinelli A, Scarlato G, Mariani C. Istituto di Clinica Neurologia, University of Milan, Italy.

Acta Neurol Scand 1994 Jul;90(1):34-8

Recent studies have suggested that patients with Parkinson's disease (PD) share many of the behavioral deficits found following lesions to the pre-frontal cortex. We assessed the performance of a group of 22 mildly impaired, not-demented parkisonians (I or II Hoehn & Yahr stage) in a test of classification and recall of pictures of familiar objects, which has been demonstrated to be sensitive to frontal damage in patients with unilateral cerebral excision. Parkinsonians utilized fewer categories than normal controls for object classification, while no significant difference was found in the immediate and delayed recall scores. These results support the contention that a subclinical dysfunction of frontal type may be present even in the early stages of PD. A subanalysis of the data suggests that this dysfunction could possibly be aggravated by anticholinergic drugs.

In vivo elevation of extracellular potassium in the rat amygdala increases extracellular glutamate and aspartate and damages neurons.

Fujikawa DG, Kim JS, Daniels AH, Alcaraz AF, Sohn TB. Experimental Neurology Laboratory, Sepulveda VA Medical Center, CA 91343, USA.

Neuroscience. 1996 Oct;74(3):695-706.

It is well known that high potassium (K+) solutions introduced by microdialysis into normal brain increase the extracellular concentration of the excitatory amino acid glutamate, and in vitro studies suggest that a high exogenously applied glutamate concentration can produce excitotoxic neuronal death. However, only

recently were in vivo studies undertaken to determine whether high-K+ exposure damages neurons. We implanted microdialysis probes into rat amygdalae bilaterally, and after a 2-h baseline period exposed one side to a modified Krebs-Ringer-bicarbonate solution containing 100 mmol/l KCl for 30,50 and 70 min, followed by a 2-h recovery period, and 70 min and 3 h without a recovery period. Of 100.9 +/- 2.0 mmol/l KCl, 12.0 +/- 1.0% was extracted by amygdalar tissue in vivo. Election of the extracellular K+ concentration in the amygdale for 70 min or longer without a recovery period produced extensive neuronal damage and edematous-appearing neuropil in the tissue dialysed, as well as loss of normal neurons. Histological evidence of edema subsided in the groups with a 2-h recovery period. Although the number of damaged neurons was not significantly higher in the group with a 70 min high-K+ exposure and 2-h recovery period, the number of normal neurons was reduced, suggesting cell loss. During 70-min high-K+ exposure, the extracellular glutamate concentration increased to 242-377% of baseline during the first 60 min, and extracellular aspartate rose to 162-213% during the first 50 min; extracellular taurine rose even higher, to 316-567% of baseline, and glutamine fell to 14-27% of baseline. Extracellular serine was decreased at 20, 50 and 70 min of high-K+ exposure; extracellular glycine was unchanged. The elevated extracellular glutamate and aspartate concentrations suggest that exposure of the amygdala to high extracellular K+ may produce cell death through an excitotoxic process, and point the way to future studies to define the specific mechanisms involved.

Dementias: the role of magnesium deficiency and an hypothesis concerning the pathogenesis of Alzheimer's disease.

Glick JL. Bionix Corporation, Potomac, Maryland 20854.

Med Hypotheses. 1990 Mar;31(3):211-25.

Evidence is presented indicating that dementias are associated with a relative insufficiency of Magnesium (Mg) in the brain. Such insufficiency may be attributable to low intake or retention of Mg; high intake of a neurotoxic metal, such as aluminum (Al), which inhibits activity of Mg-requiring enzymes; or impaired transport of Mg and/or enhanced transport of the neurotoxic metal into brain tissue. It is proposed that Alzheimer's disease (AD) involves a defective transport process, characterized by both an abnormally high incorporation of Al and an abnormally low incorporation of Mg into brain neurons. The hypothesis is advanced that an altered serum protein contributes to the progression of AD by having a greater affinity for Al than for Mg, in contrast to the normal protein, which binds Mg better than Al. The altered protein crosses the blood-brain barrier more efficiently than the normal protein and competes with the normal protein in binding to brain neurons. Binding of the altered protein to the target neurons would both facilitate Al uptake and impede Mg uptake. Evidence suggests that albumin is the serum protein that is altered.

Case-control study of early life dietary factors in Parkinson's disease.

Golbe LI, Farrell TM, Davis PH. Department of Neurology, University of Medicine and Dentistry of New Jersey, New Brunswick 08903.

Arch Neurol. 1988 Dec;45(12):1350-3.

Studies of the amyotrophic lateral sclerosis parkinsonism dementia complex of Guam direct suspicion to a heat-labile component of vegetables found in greatest concentration in seeds. We therefore surveyed patients with Parkinson's disease (PD) regarding early adult consumption of fruits and vegetables usually eaten raw, with seeds that are swallowed or scraped with the teeth. We administered a pretested questionnaire by telephone to 81 nondemented patients with PD and to a same-sex married sibling without PD. The patients and their siblings were asked whether they or their spouse (as an internal standard) had been more likely to eat each of 17 food items between marrying and age 40 years. No item was associated with the presence of PD. Unexpectedly associated with the absence of PD were preference for nuts (odds ratio, 0.39), salad oil or dressing (pressed from seeds) (odds ratio, 0.30), and plums (odds ratio, 0.24). These three items have higher vitamin E content than the other 14 items in our questionnaire. Our data are consistent with the hypothesis that vitamin E, as an antioxidant, may have prophylactic value against PD.

Effects of oral L-tyrosine administration on CSF tyrosine and homovanillic acid levels in patients with Parkinson's disease.

Growdon JH, Melamed E, Logue M, Hefti F, Wurtman RJ.

Life Sci 1982 Mar 8;30(10):827-32

To determine whether 1-tyrosine administration can enhance dopamine synthesis in humans as it does in rats, we measured levels of tyrosine and the major dopamine metabolite, homovanillic acid, in lumbar spinal fluids of 23 patients with Parkinson's disease before and during ingestion of 100 mg/kg/day of tyrosine. Nine patients took 100 mg/kg/day of probenecid in six divided doses for 24 hours prior to each spinal tap; 14 patients did not receive probenecid. L-tyrosine administration significantly increased CSF tyrosine levels in both groups of patients (p less than .01) and significantly increased homovanillic acid levels in the group of patients pretreated with probenecid (p less than .02). These data indicate that l-tyrosine administration can increase dopamine turnover in patients with disorders in which physicians wish to enhance dopaminergic neurotransmission.

Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study.

Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Institute of Social Medicine, Faculty of Medicine, Otto-von-Guericke University, Magdeburg, Germany.

Neurology 1996 Sep;47(3):644-50

In a case-control study, we compared the past dietary habits of 342 Parkinson's disease (PD) patients recruited from nine German clinics with those of 342 controls from the same neighborhood or region. Data were gathered with a structured interview and a self-administered food-frequency questionnaire. Nutrient intakes were calculated from the reported food intakes through linkage with the German Federal Food Code and analyzed using multivariate conditional logistic regression to control for total energy intake, educational status, and cigarette smoking. At the macronutrient level, patients reported higher carbohydrate intake than controls after adjustment for total energy intake, smoking, and educational status (OR = 2.74, 95% confidence interval [CI]: 1.30-6.07, for the highest versus lowest quartile, p trend = 0.02). This was reflected in higher monosaccharide and disaccharide intakes at the nutrient level. There was no difference between patients and controls in protein and fat intake after adjustment for energy intake. We found an inverse association between the intakes of beta-carotene (OR = 0.67, 95% CI: 0.37-1.19, p trend = 0.06) and ascorbic acid (OR = 0.60, 95% CI: 0.33-1.09, p trend = 0.04) by patients, although only the trend for ascorbic acid intake reached statistical significance. There was no difference between groups for alpha-tocopherol intake after adjustment for energy intake. We also found that patients reported a significantly lower intake of niacin than controls (OR = 0.15, 95% CI: 0.07-0.33, p trend < 0.00005). Our results suggest that if antioxidants play a protective role in this disease, the amounts provided by diet alone are insufficient. Although the interpretation of the inverse association between niacin intake and PD is complicated by the high niacin content in coffee and alcoholic beverages, which were also inversely associated with PD in this study, the strength of this association and its biologic plausibility warrant further investigation.

Exogenous glutamate enhances glutamate receptor subunit expression duringselective neuronal injury in the ventral arcuate nucleus of postnatal mice.

Hu L, Fernstrom JD, Goldsmith PC. Reproductive Endocrinology Center, Department of Ob/Gyn and Reproductive Sciences, University of California, San Francisco, CA 94143-0556, USA.

Neuroendocrinology. 1998 Aug;68(2):77-88.

Administration of high doses of glutamate (Glu) leads to selective neurodegeneration in discrete brain regions near circumventriclular organs of the early postnatal mouse. The arcuate nucleus-median eminence complex (ARC-ME) appears to be the most Glu-sensitive of these brain regions, perhaps because of the intimate relationships between its neurons and specialized astroglial tanycytes. To investigate the mechanism of Glu-induced neuronal loss, we administered graded doses of the sodium salt of glutamate (MSG) to postnatal mice, measured their plasma Glu concentrations, and performed microscopic analyses of the ARC-ME region 5 h after treatment. Nursing, 7-day-old mouse pups (CD1, Charles River, Hollister, Calif.) were injected subcutaneously with

single doses of 0.1-0.5 or 1.0-4.0 mg of MSG per g BW, or with water vehicle alone. Mice were decapitated 5 h later and the brains immediately fixed by immersion in buffered aldehydes. Frontal vibratome tissue sections at comparable levels of the ARC-ME were examined by light microscopy. A dose of 4.0 mg MSG/g BW caused neurodegeneration throughout the ARC region, while 1.0 mg/g MSG resulted in less extensive damage. Injection of 0.2 mg MSG/g BW, which raised plasma Glu concentrations 17-fold after 15 min, was the minimum dose tested at which nuclear and cytoplasmic changes were observed in a small group of subependymal neurons near the lateral recesses of the third ventricle. Higher doses of 0.3-0.5 mg MSG caused injury to additional neurons situated farther laterally, but damage remained confined to the ventral region of the ARC nucleus. Ultrastructural examination showed some subependymal neurons with pyknotic nuclei, reduced cytoplasmic volume, and swollen subcellular organelles, while others had fragmented and condensed nuclear material. Immunostaining for tyrosine hydroxylase indicated that dopamine neurons were spared at the threshold dose, but suffered damage after higher doses of MSG. Immunostaining for Glu receptor subtypes revealed that 0.2 mg MSG/g BW enhanced neuronal expression of NMDAR1 and of GluR2/4, and that higher doses of MSG preferentially increased NMDAR1 expression in injured neurons. These results extend previous reports of Glu sensitivity in the ARC-ME region of 7-day postnatal mice. A dose of 0.2 mg MSG/g BW s.c. causes clear but discrete injury to specific subependymal neurons of undetermined phenotype near the base of the third ventricle. Slightly higher doses of MSG evoke damage of additional neurons confined to the ventral region of the ARC traversed by tanycytes. These same greater amounts of MSG promote dose-related increase in the expression of NMDAR1 more than of GluR2/4 in injured ARC neurons, suggesting that elevated Glu receptor levels may contribute to or be related to neuronal cell death. Taken together with previous findings, the data suggest that Glu responsitivity in the ARC-ME of the postnatal mouse may result from transient developmental conditions involving the numerical ratios and juxtaposition between tanycytes and neurons, expression of Glu receptors, and perhaps other ontogenetic factors which may not persist in the mature adult.

Serum levels of coenzyme Q10 in patients with Parkinson's disease.

Jimenez-Jimenez FJ, Molina JA, de Bustos F, Garcia-Redondo A, Gomez-Escalonilla C, Martinez-Salio A, Berbel A, Camacho A, Zurdo M, Barcenilla B, Enriquez de Salamanca R, Arenas J. Department of Medicine-Neurology, University of Alcala, Alcala de Henares, Madrid, Spain. Fjimenezj@meditex.es

J Neural Transm. 2000;107(2):177-81.

We compared serum levels of coenzyme Q10 and the coenzyme Q10/cholesterol ratio in 33 patients with Parkinson's disease (PD) and 31 matched controls. The mean serum coenzyme Q10 levels did not differ significantly between the 2 study groups. Coenzyme Q10 levels were not correlated with age, age at onset, duration of the disease, scores of the Unified Parkinson Disease Rating Scale (UPDRS) or the Hoehn and Yahr staging in the PD group. The coenzyme Q10/cholesterol ratio had a significant correlation (although low) with duration of the disease (r = -

0.46), total UPDRS score (r = -0.39), motor examination of the UPDRS (r = 0.45). These values were not influenced significantly by therapy with levodopa or dopamine agonists. The normality of serum coenzyme Q10 and coenzyme Q10/cholesterol ratio suggest that these values are not related with the risk for PD.

Thiamin mono- and pyrophosphatase activities from brain homogenate of Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia patients.

Laforenza U, Patrini C, Poloni M, Mazzarello P, Ceroni M, Gajdusek DC, Garruto RM. Institute of Human Physiology, University of Pavia, Italy.

J Neurol Sci 1992 Jun;109(2):156-61

Thiamin-pyrophosphatase (TPPase) and thiamin-monophosphatase (TMPase) were determined using a spectrophotometric method at various pH values (5.5, 7.5, and 9.0) in brain tissue obtained at autopsy from amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) patients from Guam and from Guamanian patients who died from other diseases (controls). TPPase separation by thin-layer polyacrylamide gel isoelectric focusing (IEF) was also performed using both gray and white matter. TPPase content, chemically determined at pH 9.0, was found to be significantly reduced in the frontal cortex of ALS and PD patients compared to controls. TMPase content, on the contrary, was unchanged. IEF analysis showed 9 clear-cut bands with TPPase activity in the pH range 5.4-7.2 and a broad band at pH 4.7-5.2. The enzymatic activity was higher in gray than in white matter. In one patient the pattern was clearly different, with two additional bands observed at pH 7.1 and 6.7, and thought to be due to genetic microheterogeneity.

Dehydroepiandrosterone (DHEA) reduces neuronal injury in a rat model of global cerebral ischemia.

Li H, Klein G, Sun P, Buchan AM. Alberta Stroke Program, Department of Clinical Neurosciences, Foothills Hospital, University of Calgary, AB T2N 2T9, Calgary, Canada.

Brain Res. 2001 Jan 12;888(2):263-266.

Introduction: Many studies report an inverse correlation between levels of DHEA and neurological diseases. Exogenous DHEA protects hippocampal neurons against excitatory amino acid induced neurotoxicity. The purpose of this experiment is to evaluate the effect of DHEA in an animal model of transient but severe forebrain ischemia. Methods: At thirteen days prior to induction of ischemia, male Wistar rats were implanted with various doses of DHEA-placebo, 25 mg, 50 mg or 100 mg. Forebrain ischemia was induced for 10 min using a modified four-vessel occlusion technique, with hippocampal neuronal injury assessed at 7 days post-ischemically and expressed as a percentage of total cells. Results: Both normal and necrotic hippocampal CA(1) cells were counted. Percentages of hippocampal injury observed were 88+/-13% in animals treated

with placebo, 84+/-8% in the 25 mg DHEA group, and 60+/-7% in the 50 mg DHEA group. Animals treated with 100 mg DHEA displayed a significant (P<0.05) reduction of hippocampal CA(1) cell injury at 60+/-7% Conclusion: Treatment with a high dose, but not a low or moderate dose, of DHEA implantation reduces hippocampal CA(1) neuronal injury following severe but transient forebrain ischemia.

[Treatment of complicated Parkinson disease with a solution of levodopa-carbidopa and ascorbic acid] [Article in Spanish]

Linazasoro G, Gorospe A. Unidad de Trastornos del Movimiento. Clinica Quiron, San Sebastian.

Neurologia. 1995 Jun-Jul;10(6):220-3.

We prescribed a solution of levodopa-carbidopa and ascorbic acid (LCAAS) to 21 Parkinsonian patients with motor complications. Eight patients continued the treatment for a mean period of 16.8 months, experiencing substantial increases in the number of hours with good functional capacity. Bothersome symptoms such as dystonia and akathisia in off periods disappeared in all cases in which they had been present and LCAAS was tolerated (in 6 of the 8 patients who continued in the study and in 4 who abandoned treatment late). Intake of other anti-Parkinsonian drugs was reduced. Thirteen patients abandoned the study, citing exacerbation of biphasic dyskinesia as the main reason. We conclude that LCAAS is a useful therapy in some Parkinsonian patients whose motor complications are not managed with conventional drug treatment. Screening of patients is probably of utmost importance to ensure that LCAAS is not administered to patients who already suffer intense biphasic dyskinesia.

Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study.

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Ann Neurol 1996 Jan;39(1):89-94

Oxidative stress plays an important role in the pathogenesis of Parkinson's disease (PD). In a population-based, case-control study we examined whether dietary intake of antioxidants and other oxidative compounds was associated with PD. Dietary intake was assessed by a semiquantitative food-frequency questionnaire in 110 PD case patients and 287 control subjects. A higher caloric intake was observed in patients with PD and did not vary with increasing duration of symptoms. Energy-adjusted fat intake was significantly higher among patients with PD than control subjects (p for trend = 0.007). Intake of protein (p for trend = 0.17) and carbohydrates (p for trend = 0.46) did not differ in patients and control subjects. Analyses of the primary sources of fat indicated that increasing intake of animal fats were strongly related to PD (odds ratio, 5.3; 95% confidence interval, 1.8-15.5; p for trend = 0.001). No significant differences were observed

for intake of vitamins with antioxidant activity. An increase in the consumption of animal fats among patients with PD is consistent with the hypothesis that oxidative stress and lipid peroxidation are important in the pathogenesis of this disease. No effect of vitamins with antioxidant activity, either from food or supplements, was observed.

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects.

Matthews RT, Yang L, Browne S, Baik M, Beal MF. Neurochemistry Laboratory, Neurology Service, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA.

Proc Natl Acad Sci U S A. 1998 Jul 21;95(15):8892-7.

Coenzyme Q10 is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Feeding with coenzyme Q10 increased cerebral cortex concentrations in 12- and 24-month-old rats. In 12-month-old rats administration of coenzyme Q10 resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q10. Oral administration of coenzyme Q10 markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q10 increases both brain and brain mitochondrial concentrations. They provide further evidence that coenzyme Q10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.

The role of glutamatergic transmission in the pathogenesis of levodopa-induced dyskinesias. Potential therapeutic approaches.

Merims D, Ziv I, Sherki Y, Djaldetti R, Melamed E. Department of Neurology, Rabin Medical Center, Belinson Campus, Petah Tikva.

Neurol Neurochir Pol. 2001;35 Suppl 3:65-8.

Dyskinesias are the most frequent adverse effect of chronic levodopa therapy in patients with Parkinson's disease (PD). Current pharmacological treatment for this problem is unsatisfactory. Recently, there is evidence for the role of glutamate in the basal ganglia neuronal circuitry in the generation of dyskinesias. If indeed glutamatergic overactivity beyond the dopaminergic synapses plays a role in the pathogenesis of these involuntary movements, there is hope that its suppression may be beneficial without causing loss of levodopa efficacy and parkinsonian deterioration. Indeed, NMDA receptor antagonists such as amantadine and dextrometorphan can reduce such dyskinesias. We tested the efficacy of riluzole, an inhibitor of glutamatergic transmission in the inhibition of levodopa-induced dyskinesias.

Rotations induced by L-dopa in parkinsonian rats are reduced by an ingestion of amino acids.

Mizuta E, Kuno S. Department of Neurology, Utano National Hospital, Kyoto, Japan.

J Neural Transm Park Dis Dement Sect. 1993;6(3):211-4.

We studied the effect of amino acid load on L-dopa-induced rotational behavior in rats with unilateral lesion of the nigrostriatal pathway. Pretreatment of rats with an ingestion of high concentration of amino acids significantly reduced the number of rotations induced by subcutaneously injected L-dopa. These results provide the experimental basis for clinical observations that dietary protein affects the response to L-dopa in parkinsonian patients.

Influence of reduced nicotinamide adenine dinucleotide on the production of interleukin-6 by peripheral human blood leukocytes.

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Neuroimmunomodulation. 2001;9(4):203-8.

OBJECTIVE: Recently, therapy with nicotinamide adenine dinucleotide (NADH) revealed positive effects on neurodegenerative disorders associated with inflammation of the CNS, such as Parkinson's disease or Alzheimer's disease. Pathophysiologically, focal CNS inflammation seems to be accompanied by an unbalanced cytokine production, pointing to an involvement of the immune system. Therefore, the aim of our study was to investigate whether NADH could influence cytokine release of peripheral blood leukocytes (PBLs) with special reference to interleukin-6 (IL-6).

METHODS: PBLs from 18 healthy donors were incubated in vitro with different concentrations of NADH to generate dose-response curves. As a control, mitogen-treated cells and unstimulated cells were included.

RESULTS: In PBLs from the 18 healthy donors, NADH significantly stimulated the dose-dependent release of IL-6, ranging from 6.25 to 400 microg/ml, compared to medium-treated cells (p < 0.001). An amount of 1,000 pg/ml IL-6 was induced by NADH concentrations ranging from 3.1 to >25 microg/ml.

CONCLUSIONS: It is concluded that NADH possesses cytokine-modulating effects on peripheral blood cells. The biological relevance of these data is discussed in the context of the recent use of NADH for the treatment of several neurodegenerative disorders. Copyright 2002 S. Karger AG, Basel

Toxic effects of L-DOPA on mesencephalic cell cultures: protection with antioxidants.

Pardo B, Mena MA, Casarejos MJ, Paino CL, De Yebenes JG. Departamento de Investigacion, Hospital Ramon y Cajal, Madrid, Spain.

Brain Res. 1995 Jun 5;682(1-2):133-43.

The toxicity of L-3,4-dihydroxyphenylalanine (L-DOPA) was studied in neuronal cultures from rat mesencephalon. The survival and function of DA neurons were assessed by the number of tyrosine hydroxylase-positive (TH+) cells and 3H-DA uptake and those non-DA neurons by the exclusion of Trypan blue and the high-affinity 3H-GABA uptake. L-DOPA was toxic for both DA and non-DA neurons. DA neurons were more severely affected than non-DA neurons after short periods of treatment and with exposure to a low dose of L-DOPA (25 vs. 100 microM) and less selectively affected after 1 or 2 days of treatment. After incubation with L-DOPA, a disruption of the neuritic network and an overall deterioration were observed, more evident for TH+ cells in the whole culture. Auto-oxidation to quinones is responsible in part for L-DOPA toxicity in non-DA neurons since the levels of quinones correlated well with the severity of cell death in the cultures. The damage of DA neurons took place before the rising of quinones, suggesting that quinones are not essential in L-DOPA toxicity for DA neurons. Antioxidants, such as ascorbic acid and sodium metabisulfite, completely prevented L-DOPA-induced quinone formation as well as the death of non-DA neurons. In contrast, they could only partially prevent the damage produced by L-DOPA in DA neurons. Mazindol, a selective inhibitor of DA uptake, protected TH+ cells from L-DOPA.

L-tryptophan administration in L-dopa-induced hallucinations in elderly Parkinsonian patients.

Rabey JM, Vardi J, Askenazi JJ, Streifler M.

Gerontology. 1977;23(6):438-44.

L-tryptophan (L-T) was added at a dose of 150-450 mg daily to eight Parkinsonian patients who developed visual hallucinations with paranoidal features under L-dopa (L-D) treatment (112.5-75 mg daily) in combination with alpha-methyldopa hydrazine (12.5-75 mg daily). In six patients L-T ameliorated the symptomatology by arresting the visual paranoidal hallucinations or diminishing their frequency and relieving the psychomotor agitation. As a 'side effect', L-T produced new 'pleasurable', 'LSD-like' visual images in three patients. In two patients, in whom L-T did not affect the mental disturbances, amelioration was obtained only by phenothiazines. Theoretical considerations on the role of dopamine in the genesis of visual hallucinations and mental disturbances emphasizes the benefit of L-T administration in this 'organomental' syndrome.

L-dopa competes with tyrosine and tryptophan for human brain uptake.

Riederer P.

Nutr Metab. 1980;24(6):417-23.

Tyrosine and tryptophan have been assayed spectrofluorometrically in postmortem human brain areas of patients with Parkinson's disease treated orally with or without 3,4-dihydroxyphenylalanine (L-dopa) plus the peripherally acting decarboxylase inhibitor benserazide. Tyrosine as well as tryptophan decrease significantly after treatment with L-dopa, thus showing a competitive action of L-dopa to other aromatic amino acids on human brain uptake. It is suggested that some of the side effects of L-dopa treatment in Parkinson's disease are due to a disturbance in the brain and neural uptake of other, specially aromatic and branched-chain amino acids. An influence of L-dopa administration on protein synthesis also cannot be excluded.

Neuroprotective effect of vitamin E on the early model of Parkinson's disease in rat: behavioral and histochemical evidence.

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Brain Res. 2001 Feb 16;892(1):211-7.

There is strong evidence that oxidative stress participates in the etiology of Parkinson's disease (PD). We designed this study to investigate the neuroprotective effect of vitamin E in the early model of PD. For this purpose, unilateral intrastriatal 6-hydroxydopamine (12.5 microg/5 microl) lesioned rats were pretreated intramuscularly with D-alpha-tocopheryl acid succinate (24 I.U./kg, i.m.) 1 h before and three times per week for 1 month post-surgery. Apomorphine- and amphetamine-induced rotational behavior was measured postlesion fortnightly. A parallel tyrosine hydroxylase immunoreactivity and wheat germ agglutinin-horse radish peroxidase (WGA-HRP) tract-tracing study was performed to evaluate the vitamin E pretreatment efficacy. Tyrosine hydroxylase-immunohistochemical analyses showed a reduction of 18% in ipsilateral substantia nigra pars compacta (SNC) cell number of the vitamin E-pretreated lesioned (L+E) group comparing with contralateral side. The cell number dropped to 53% in the lesioned (L+V) group. In addition, retrograde-labeled neurons in ipsilateral SNC were reduced by up to 30% in the L+E group and 65% in the L+V group. Behavioral tests revealed that there are 74% and 68% reductions in contraversive and ipsiversive rotations in the L+E group, respectively, as compared with the L+V group. Therefore repeated intramuscular administration of vitamin E exerts a rapid protective effect on the nigrostriatal dopaminergic neurons in the early unilateral model of PD.

Interaction between sodium ascorbate and dopamine.

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Free Radic Biol Med. 1998 Dec;25(9):1013-20.

The interaction between sodium ascorbate and dopamine was investigated by three different parameters: radical intensity, prooxidant action, and cytotoxicity induction. Sodium ascorbate and dopamine produced the doublet and quartet ESR signals under alkaline conditions (pH 8.0-9.5), respectively. Addition of increasing concentrations of sodium ascorbate completely scavenged the dopamine radical and replaced the latter with its own radical. Similarly, dopamine slightly, but significantly reduced the radical intensity of sodium ascorbate. These two compounds stimulated the methionine oxidation and hydrogen peroxide generation in culture medium, but in combination, their stimulation activities were weakened. Both of these two compounds dose-dependently reduced the viable cell number of human oral squamous carcinoma HSC-4 cells, and their cytotoxic activity was significantly reduced by catalase. When these two compounds were mixed together before adding to HSC-4 cells, both of their cytotoxic activities were diminished. The present study demonstrates the interaction between sodium ascorbate and dopamine, which might modify their biological activities and generation of nerve disorders such as Parkinson's disease.

L-tryptophan in neuropsychiatric disorders: a review.

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Int J Neurosci. 1992 Nov-Dec;67(1-4):127-44.

Animal data indicate that serotonin (5-HT) is a major neurotransmitter involved in the control of numerous central nervous system functions including mood, aggression, pain, anxiety, sleep, memory, eating behavior, addictive behavior, temperature control, endocrine regulation, and motor behavior. Moreover, there is evidence that abnormalities of 5-HT functions are related to the pathophysiology of diverse neurological conditions including Parkinson's disease, tardive dyskinesia, akathisia, dystonia, Huntington's disease, familial tremor, restless legs syndrome, myoclonus, Gilles de la Tourette's syndrome, multiple sclerosis, sleep disorders, and dementia. The psychiatric disorders of schizophrenia, mania, depression, aggressive and self-injurious behavior, obsessive compulsive disorder, seasonal affective disorder, substance abuse, hypersexuality, anxiety disorders, bulimia, childhood hyperactivity, and behavioral disorders in geriatric patients have been linked to impaired central 5-HT functions. Tryptophan, the natural amino acid precursor in 5-HT biosynthesis, increases 5-HT synthesis in the brain and, therefore, may stimulate 5-HT release and function. Since it is a natural constituent of the diet, tryptophan should have low toxicity and produce few side effects. Based on these advantages, dietary tryptophan supplementation has been used in the management of neuropsychiatric disorders with variable success. This review summarizes current clinical use of tryptophan supplementation in neuropsychiatric disorders.

L-tryptophan supplementation in Parkinson's disease.

Sandyk R, Fisher H. Department of Neurology, University of Arizona, Tucson 85724.

Int J Neurosci. 1989 Apr;45(3-4):215-9.

Two female Parkinsonian patients with levodopa-induced "On-Off" responded dramatically to administration of L-tryptophan supplementation. This report highlights the role of serotonergic deficiency in the pathophysiology of Parkinson's disease and of levodopa-induced motor fluctuations, and suggests that L-tryptophan supplementation may be useful in ameliorating motor complications of chronic levodopa therapy in the disease. The possibility that L-tryptophan supplementation with initiation of levodopa therapy may be useful in preventing levodopa-induced motor complications is discussed.

Pyridoxine improves drug-induced parkinsonism and psychosis in a schizophrenic patient.

Sandyk R, Pardeshi R. Department of Psychiatry College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, NY 10032.

Int J Neurosci. 1990 Jun;52(3-4):225-32.

Drug-induced Parkinsonism is a common serious side-effect of neuroleptic therapy. In cases of irreversible drug-induced Parkinsonism, pharmacological management is notoriously difficult. A schizophrenic patient with severe neuroleptic-induced Parkinsonism and Tardive Dyskinesia is presented in whom administration of pyridoxine (vitamin B6) (100 mg/d) resulted in dramatic and persistent attenuation of the movement disorders as well as reduction of psychotic behavior. Since pyridoxine deficiency is associated with marked reduction of cerebral serotonin concentrations and pineal melatonin production in rats, the effects of pyridoxine on the movement disorder and psychosis may have been mediated largely by enhancing serotonin and melatonin functions. An additional effect of excess pyridoxine administration on GABA and dopamine activity cannot be excluded. Pyridoxine has been reported to attenuate the severity of levodopa-induced dyskinesias in patients with Parkinson's disease and it is suggested that pyridoxine supplementation should be considered in psychiatric patients with drug-induced movement disorders including persistent Parkinsonism. An underlying pyridoxine deficiency in these patients may exacerbate the psychotic behavior and additionally, potentially increase the risk of drug-induced movement disorders.

Coenzyme Q10 and nicotinamide and a free radical spin trap protect against MPTP neurotoxicity.

Schulz JB, Henshaw DR, Matthews RT, Beal MF. Neurochemistry Laboratory, Massachusetts General Hospital, Boston 02114, USA.

Exp Neurol. 1995 Apr;132(2):279-83.

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) produces Parkinsonism in both experimental animals and in man. MPTP is metabolized to 1-methyl-4-

phenylpridinium, an inhibitor of mitochondrial complex I. MPTP administration produces ATP depletions in vivo, which may lead to secondary excitotoxicity and free radical generation. If this is the case then agents which improve mitochondrial function or free radical scavengers should attenuate MPTP neurotoxicity. In the present experiments three regimens of MPTP administration produced varying degrees of striatal dopamine depletion. A combination of coenzyme Q10 and nicotinamide protected against both mild and moderate depletion of dopamine. In the MPTP regimen which produced mild dopamine depletion nicotinamide or the free radical spin trap N-tert-butyl-alpha-(2-sulfophenyl)-nitrone were also effective. There was no protection with a MPTP regimen which produced severe dopamine depletion. These results show that agents which improve mitochondrial energy production (coenzyme Q10 and nicotinamide) and free radical scavengers can attenuate mild to moderate MPTP neurotoxicity.

Ascorbic acid stimulates DOPA synthesis and tyrosine hydroxylase gene expression in the human neuroblastoma cell line SK-N-SH.

Seitz G, Gebhardt S, Beck JF, Bohm W, Lode HN, Niethammer D, Bruchelt G. Department of Hematology and Oncology, Children's Hospital, University of Tubingen, Germany.

Neurosci Lett. 1998 Mar 6;244(1):33-6.

Ascorbic acid is well known to induce noradrenaline synthesis in sympathetic nervous cells. In a series of experiments we found that incubation of the neuroblastoma cell line SK-N-SH with ascorbic acid (100-500 microM) for 2 h results in a significantly enhanced synthesis of 3,4-dihydroxyphenylalanine (DOPA) and dopamine. Additionally, cDNA-polymerase chain reaction (cDNA-PCR) analysis of relative mRNA levels corresponding to the enzymes involved in catecholamine synthesis revealed a 3-fold increase of tyrosine hydroxylase gene expression after 5 days of incubation with ascorbic acid (200 microM), whereas expression of dopamine-beta-hydroxylase was found to be unaltered. In summary the data give evidence that ascorbic acid leads to enhanced DOPA production in SK-N-SH cells by two different mechanisms: at the metabolic level after short-term incubation and by increasing the tyrosine hydroxylase gene expression after long-term incubation. Based on these data we suppose that enhancement of DOPA synthesis by ascorbic acid may be useful in the treatment of early Parkinson's disease.

Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects.

Shults CW, Haas RH, Passov D, Beal MF. Neurology Service, Veterans Affairs Medical Center, San Diego, CA 92161, USA.

Ann Neurol. 1997 Aug;42(2):261-4.

The activities of complex I and complex II/III in platelet mitochondria are reduced in patients with early, untreated Parkinson's disease. Coenzyme Q10 is the electron acceptor for complex I and complex II. We found that the level of coenzyme Q10 was significantly lower in mitochondria from parkinsonian patients than in mitochondria from age- and sex-matched control subjects and that the levels of coenzyme Q10 and the activities of complex I and complex II/III were significantly correlated.

Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients.

Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH. Department of Neurosciences, University of California, San Diego, La Jolla, USA.

Neurology. 1998 Mar;50(3):793-5.

We report a pilot study of three oral doses of coenzyme Q10 (CoQ10) (200 mg administered two, three, or four times per day for 1 month) in 15 subjects with Parkinson's disease. Oral CoQ10 caused a substantial increase in the plasma CoQ10 level. It was well tolerated, but at the highest dose (200 mg four times per day) mild, transient changes in the urine were noted. CoQ10 did not change the mean score on the motor portion of the Unified Parkinson's Disease Rating Scale. There was a trend toward an increase in complex I activity in the subjects.

A possible role of coenzyme Q10 in the etiology and treatment of Parkinson's disease.

Shults CW, Haas RH, Beal MF. Department of Neurosciences, University of California, San Diego, La Jolla 92093, USA.

Biofactors. 1999;9(2-4):267-72.

Parkinson's disease (PD) is a degenerative neurological disorder. Recent studies have demonstrated reduced activity of complex I of the electron transport chain in brain and platelets from patients with PD. Platelet mitochondria from parkinsonian patients were found to have lower levels of coenzyme Q10 (CoQ10) than mitochondria from age/sex-matched controls. There was a strong correlation between the levels of CoQ10 and the activities of complexes I and II/III. Oral CoQ10 was found to protect the nigrostriatal dopaminergic system in one-year-old mice treated with MPTP, a toxin injurious to the nigrostriatal dopaminergic system. We further found that oral CoQ10 was well absorbed in parkinsonian patients and caused a trend toward increased complex I activity. These data suggest that CoQ10 may play a role in cellular dysfunction found in PD and may be a potential protective agent for parkinsonian patients.

Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline.

Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M; Parkinson Study Group. Department of Neurosciences, Mail Code 0662, University of California-San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0662, USA. cshults@ucsd.edu

Arch Neurol. 2002 Oct;59(10):1541-50.

BACKGROUND: Parkinson disease (PD) is a degenerative neurological disorder for which no treatment has been shown to slow the progression.

OBJECTIVE: To determine whether a range of dosages of coenzyme Q10 is safe and well tolerated and could slow the functional decline in PD.

DESIGN: Multicenter, randomized, parallel-group, placebo-controlled, double-blind, dosage-ranging trial.

SETTING: Academic movement disorders clinics.

PATIENTS: Eighty subjects with early PD who did not require treatment for their disability.

INTERVENTIONS: Random assignment to placebo or coenzyme Q10 at dosages of 300, 600, or 1200 mg/d.

MAIN OUTCOME MEASURE: The subjects underwent evaluation with the Unified Parkinson Disease Rating Scale (UPDRS) at the screening, baseline, and 1-, 4-, 8-, 12-, and 16-month visits. They were followed up for 16 months or until disability requiring treatment with levodopa had developed. The primary response variable was the change in the total score on the UPDRS from baseline to the last visit.

RESULTS: The adjusted mean total UPDRS changes were +11.99 for the placebo group, +8.81 for the 300-mg/d group, +10.82 for the 600-mg/d group, and +6.69 for the 1200-mg/d group. The P value for the primary analysis, a test for a linear trend between the dosage and the mean change in the total UPDRS score, was.09, which met our prespecified criteria for a positive trend for the trial. A prespecified, secondary analysis was the comparison of each treatment group with the placebo group, and the difference between the 1200-mg/d and placebo groups was significant (P =.04).

CONCLUSIONS: Coenzyme Q10 was safe and well tolerated at dosages of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q10 than in those assigned to placebo, and the benefit was greatest in subjects receiving the highest dosage. Coenzyme Q10 appears to slow the progressive deterioration of function in PD, but these results need to be confirmed in a larger study.

Autoxidation and neurotoxicity of 6-hydroxydopamine in the presence of some antioxidants: potential implication in relation to the pathogenesis of Parkinson's disease.

Soto-Otero R, Mendez-Alvarez E, Hermida-Ameijeiras A, Munoz-Patino AM, Labandeira-Garcia JL. Departamento de Bioquimica y Biologia Molecular, Facultad de Medicina, Universidad de Santiago de Compostela, Spain. bnsoto@uscmail.usc.es

J Neurochem. 2000 Apr;74(4):1605-12.

6-Hydroxydopamine (6-OHDA) is a dopaminergic neurotoxin putatively involved in the pathogenesis of Parkinson's disease (PD). Its neurotoxicity has been related to the production of reactive oxygen species. In this study we examine the effects of the antioxidants ascorbic acid (AA), glutathione (GSH), cysteine (CySH), and N-acetyl-CySH (NAC) on the autoxidation and neurotoxicity of 6-OHDA. In vitro, the autoxidation of 6-OHDA proceeds rapidly with the formation of H2O2 and with the participation of the H2O2 produced in the reaction. The presence of AA induced a reduction in the consumption of O2 during the autoxidation of 6-OHDA and a negligible presence of the p-quinone, which demonstrates the efficiency of AA to act as a redox cycling agent. The presence of GSH, CySH, and NAC produced a significant reduction in the autoxidation of 6-OHDA. In vivo, the presence of sulfhydryl antioxidants protected against neuronal degeneration in the striatum, which was particularly remarkable in the case of CySH and was attributed to its capacity to remove the H2O2 produced in the autoxidation of 6-OHDA. These results corroborate the involvement of oxidative stress as the major mechanism in the neurotoxicity of 6-OHDA and the putative role of CySH as a scavenger in relation to PD.

[Intestinal microflora and concomitant gastrointestinal diseases in patients with chronic hepatitis B and C] [Article in Russian]

Sozinov AS, Anikhovskaia IA, Baiazitova LT, Enaleeva DSh, Zinkevich OD, Salakhov IM, Tkacheva SV, Likhoded VG. State Medical University, Research Institute of Epidemiology and Microbiology, Kazan, Russia.

Zh Mikrobiol Epidemiol Immunobiol. 2002 Jan-Feb;(1):61-4.

In chronic viral hepatitis B and C the development of intestinal dysbacteriosis and high occurrence of concomitant diseases of the gastrointestinal tract were observed. In cases of increased dysbacteriosis degree and in the presence of concomitant diseases the blood plasma of patients exhibited higher activity in reaction with the of amebocytes lysate obtained from crabs of the genus Limulus. A suggestion was made that the endotoxin of Gram negative intestinal microflora could probably play some role in the development of pathological processes in chronic viral hepatitis B and C.

Effect of antimicrobial agents on the ecological balance of human microflora.

Sullivan A, Edlund C, Nord CE. Department of Microbiology, Pathology, and Immunology, Huddinge University Hospital, Karolinska Institutet, and Soderkoping Hogskola, Stockholm, Sweden.

Lancet Infect Dis. 2001 Sep;1(2):101-14.

The normal microflora acts as a barrier against colonisation of potentially pathogenic microorganisms and against overgrowth of already present opportunistic microorganisms. Control of growth of opportunistic microorganisms is termed colonisation resistance. Administration of antimicrobial agents, therapeutically or as prophylaxis, causes disturbances in the ecological balance between the host and the normal microflora. Most studies on the impact of antimicrobial agents on normal microflora have been carried out on the intestinal flora. Less is known on the effects on oropharyngeal, skin, and vaginal microflora. Disturbances in the microflora depend on the properties of the agents as well as of the absorption, route of elimination, and possible enzymatic inactivation and/or binding to faecal material of the agents. The clinically most common disturbances in the intestinal microflora are diarrhoea and fungal infections that usually cease after the end of treatment. A well-balanced microflora prevents establishment of resistant microbial strains. By using antimicrobial agents that do not disturb colonisation resistance, the risk of emergence and spread of resistant strains between patients and dissemination of resistant determinants between microorganisms is reduced. In this article, the potential ecological effects of administration of antimicrobial agents on the intestinal, oropharyngeal, and vaginal microflora are summarised. The review is based on clinical studies published during the past 10 years.

Parkin is linked to the ubiquitin pathway.

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J Mol Med. 2001 Sep;79(9):482-94.

Autosomal recessive juvenile parkinsonism (AR-JP) is one of the most common forms of familial Parkinson's disease. AR-JP is characterized by selective and massive loss of dopaminergic neurons in the substantia nigra of the midbrain and absence of Lewy bodies, the pathological hallmark of idiopathic Parkinson's disease. Parkin, the causative gene of AR-JP, encodes a 52-kDa protein that is a RING-type ubiquitin (Ub) protein ligase (E3) collaborating with a Ub-conjugating enzyme (E2) belonging to a cognate class of UbcH7 or UbcH8. Analysis of parkin mutations in AP-JP patients reveals that the functional loss of parkin as an E3 enzyme is the molecular basis of AR-JP. Thus it is now clear that AR-JP is due to failure of proteolysis mediated by the Ub-proteasome system and accumulation of as yet unidentified protein(s) causes nigral neuronal death without formation of Lewy bodies. These findings should shed new light on the mechanisms underlying neurodegeneration in sporadic Parkinson's disease as well as AR-JP.

Role of human microflora in health and disease.

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Eur J Clin Microbiol Infect Dis. 1992 Nov;11(11):1012-5.

The human host and its microbial flora constitute a complex ecosystem whose equilibrium serves as a remarkable example of reciprocal adaptation. Intestinal bacteria play an important role in the development of the immune system. The normal intestinal flora is responsible for resistance to colonization by exogenous pathogenic microorganisms. Nevertheless, it also constitutes a reservoir of potentially pathogenic bacteria in close contact with the host. These bacteria are responsible for opportunistic infections in immunocompromised hosts. The equilibrium of the flora can be upset by antibiotics, leading to infections as a result of proliferation of antibiotic-resistant pathogenic bacteria.

Ceroid/lipofuscin-loaded human fibroblasts show decreased survival time and diminished autophagocytosis during amino acid starvation.

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Exp Gerontol. 1999 Dec;34(8):943-57.

To test whether heavy accumulation of ceroid/lipofuscin can disturb important functions of the lysosomal system, AG-1518 human fibroblasts, ceroid/lipofuscin-loaded (following prolonged culture at normobaric hyperoxia) or not, were exposed to amino acid starvation. Ceroid/lipofuscin-loading resulted in decreased cellular survival. Also, there was an inverse relationship between amounts of ceroid/lipofuscin and the survival time of individual cells within the same cultures. Ceroid/lipofuscin-loaded fibroblasts displayed diminished autophagocytotic capacity, as demonstrated by electron microscopy and by treatment of cell cultures with NH4Cl (which inhibits autophagocytotic degradation by increasing intralysosomal pH) for 1 week before ensuing starvation. The latter treatment increased survival of control cells (due to deposition of nondegraded autophagocytosed material before start of starvation), but not that of ceroid/lipofuscin-loaded cells. Moreover, when NH4Cl treatment was combined with starvation, both groups of cells showed approximately the same shortened survival times, testifying to the causal relationship between diminished autophagocytosis and decreased survival of starving ceroid/lipofuscin-loaded cells. We hypothesize that large amounts of undegradable ceroid/lipofuscin within the acidic vacuolar compartment may interfere with lysosomal function, resulting in poor renewal of long-lived proteins and worn-out/damaged organelles, decreased adaptability, and cell death.

Modulation of the host flora.

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Eur J Clin Microbiol Infect Dis. 1989 Jan;8(1):1-7.

Modulation of the bacterial flora of patients with a high risk of acquiring an infection can be achieved in several ways. The approach used in the Leiden University Hospital is based on selective elimination of the aerobic bacteria in the oropharyngeal cavity and intestinal tract, leaving the anaerobic flora intact. This kind of selective modulation of the host flora has an advantage in that it does not affect the colonization resistance provided by bacterial antagonism, which prevents colonization by resistant but potentially pathogenic bacteria or fungi. The elimination of aerobic bacteria combined with nursing in protective isolation and consumption of food with few bacteria has led to a significant reduction of the incidence of major and fatal infections in patients during episodes of severe granulocytopenia. From these results it may be concluded that the objective of selective antibiotic modulation, namely, the prevention of infections, can be achieved with this approach.

Chronic low-dose glutamate is toxic to retinal ganglion cells. Toxicity blocked by memantine.

Vorwerk CK, Lipton SA, Zurakowski D, Hyman BT, Sabel BA, Dreyer EB. Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA 02114, USA.

Invest Ophthalmol Vis Sci. 1996 Jul;37(8):1618-24.

PURPOSE: It is well known that acute exposure to high concentrations of glutamate is toxic to central mammalian neurons. However, the effect of a chronic, minor elevation over endogenous glutamate levels has not been explored. The authors have suggested that such chronic exposure may play a role in glaucomatous neuronal loss. In the current study, they sought to explore whether a chronic, low-dose elevation in vitreal glutamate was toxic to retinal ganglion cells and whether this toxicity could be prevented with memantine, a glutamate antagonist.

METHODS: Rats were injected serially and intravitreally with glutamate to induce chronic elevations in glutamate concentration. A second group of rats was treated with intraperitoneal memantine and glutamate. Control groups received vehicle injection with or without concurrent memantine therapy. After 3 months, the animals were killed, and ganglion cell survival was evaluated.

RESULTS: Intravitreal injections raised the intravitreal glutamate levels from an endogenous range of 5 to 12 microM glutamate to 26 to 34 microM. This chronic glutamate elevation killed 42% of the retinal ganglion cells after 3 months. Memantine treatment alone had no effect on ganglion cell survival. However, when memantine was given concurrently with low-dose glutamate, memantine was partially protective against glutamate toxicity.

CONCLUSIONS: These data suggest that minor elevations in glutamate concentration can be toxic to ganglion cells if this elevation is maintained for 3

months. Furthermore, memantine is efficacious at protecting ganglion cells from chronic low-dose glutamate toxicity.

Calcium and vitamin D metabolism in Guamanian Chamorros with amyotrophic lateral sclerosis and parkinsonism-dementia.

Yanagihara R, Garruto RM, Gajdusek DC, Tomita A, Uchikawa T, Konagaya Y, Chen KM, Sobue I, Plato CC, Gibbs CJ Jr.

Ann Neurol 1984 Jan;15(1):42-8

We evaluated 16 Guamanian Chamorros with amyotrophic lateral sclerosis and 33 patients with parkinsonism-dementia for disturbances of calcium and vitamin D metabolism. The serum immunoreactive parathyroid hormone level was mildly elevated in 6 patients with amyotrophic lateral sclerosis and in 5 patients with parkinsonism-dementia. There were significant positive correlations between serum immunoreactive parathyroid levels and duration of illness in male patients with motor neuron disease, but not in female patients or in patients with parkinsonism-dementia. Intestinal absorption of calcium, as assessed by serum and urinary activity of calcium 47 following oral administration, was decreased in 2 patients with amyotrophic lateral sclerosis and in 4 patients with parkinsonism-dementia, all of whom had low levels of serum 1,25-dihydroxyvitamin D. Reductions in cortical bone mass were striking in patients with motor neuron disease. A significant negative correlation was found between the percentage of cortical area of the second metacarpal bone and muscle atrophy and weakness, and significant positive correlations were found between degree of immobility and ratio of urinary hydroxyproline to creatinine in patients with amyotrophic lateral sclerosis and parkinsonism-dementia. In general, abnormalities in calcium metabolism were subtle. Thus, if the demonstrated deposition of metals, particularly calcium and aluminum, in central nervous system tissues of Guamanians with these two conditions is a cause of the diseases and of the early appearance of neurofibrillary tangles in neurons, the accumulation has apparently occurred long before onset of symptoms, and detectable abnormalities of calcium and vitamin D metabolism may already have been corrected.

Detection of subclinical ascorbate deficiency in early Parkinson's disease.

Yapa SC. Bury Health Authority, Lancs.

Public Health. 1992 Sep;106(5):393-5.

From mid-October 1989 to mid-July 1990 all newly admitted residents to Bury Local Authority Residential Homes were comprehensively medically screened. In a series of 100 residents eight had early Parkinson's disease (six of them hitherto undiagnosed). Seven showed evidence of Vitamin C deficiency. Of the seven showing evidence of deficiency, four suffered from early Parkinson's disease. Of the 93 without evidence of Vitamin C deficiency only four had Parkinson's disease. This indicates a significantly higher prevalence of Parkinson's disease in the group with Vitamin C deficiency (P less than 0.001 using Fisher's exact).

Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting.

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Cell Mol Neurobiol. 2001 Dec;21(6):605-16.

To review the interaction between melatonin and the dopaminergic system in the hypothalamus and striatum and its potential clinical use in dopamine-related disorders in the central nervous system. Medline-based search on melatonin-dopamine interactions in mammals. Melatonin. the hormone produced by the pineal gland at night. influences circadian and seasonal rhythms, most notably the sleep-wake cycle and seasonal reproduction. The neurochemical basis of these activities is not understood yet. Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla-pons, and retina). Antidopaminergic activities of melatonin have been demonstrated in the striatum. Dopaminergic transmission has a pivotal role in circadian entrainment of the fetus, in coordination of body movement and reproduction. Recent findings indicate that melatonin may modulate dopaminergic pathways involved in movement disorders in humans. In Parkinson patients melatonin may, on the one hand, exacerbate symptoms (because of its putative interference with dopamine release) and, on the other, protect against neurodegeneration (by virtue of its antioxidant properties and its effects on mitochondrial activity). Melatonin appears to be effective in the treatment of tardive dyskinesia. a severe movement disorder associated with long-term blockade of the postsynaptic dopamine D2 receptor by antipsychotic drugs in schizophrenic patients. The interaction of melatonin with the dopaminergic system may play a significant role in the nonphotic and photic entrainment of the biological clock as well as in the fine-tuning of motor coordination in the striatum. These interactions and the antioxidant nature of melatonin may be beneficial in the treatment of dopamine-related disorders.

24. Thyroid Deficiency

Preventative and curative options include:

Vitamin A, vitamin B complex, vitamin B12, vitamin C, vitamin E, coenzyme Q10, magnesium, manganese, selenium, zinc, tyrosine, DHEA, soy protein

Use of soy protein supplement and resultant need for increased dose of levothyroxine.

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Endocr Pract 2001 May-Jun;7(3):193-4

Objective: To report a case of difficulty in achieving suppressive serum levels of thyroid hormone because of malabsorption of exogenous levothyroxine attributable to daily ingestion in close temporal relationship to the intake of a soy protein-containing food supplement. Methods: We present the relevant history and laboratory data of the current case and provide supportive documentation from the literature. Results: A 45-year-old woman who had hypothyroidism after a near-total thyroidectomy and radioactive iodine ablative therapy for papillary carcinoma of the thyroid required unusually high oral doses of levothyroxine to achieve suppressive serum levels of free thyroxine (T4) and thyrotropin (thyroid-stimulating hormone or TSH). She had routinely been taking a "soy cocktail" protein supplement immediately after her levothyroxine. Temporal separation of the intake of the soy protein cocktail from the administration of the levothyroxine resulted in attainment of suppressive serum levels of free T4 and TSH with use of lower doses of levothyroxine. Conclusion: Administration of levothyroxine concurrently with a soy protein dietary supplement results in decreased absorption of levothyroxine and the need for higher oral doses of levothyroxine to attain therapeutic serum thyroid hormone levels.

Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism.

Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Institute of Endocrinology, Kaunas Medical University, Lithuania.

N Engl J Med. 1999 Feb 11;340(6):424-9.

BACKGROUND: Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown.

METHODS: We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 microg of the usual dose of thyroxine was replaced by 12.5 microg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period.

RESULTS: The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone-binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments.

CONCLUSIONS: In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

Homocysteine, hypothyroidism, and effect of thyroid hormone replacement.

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Thyroid. 1999 Dec;9(12):1163-6.

Elevation of total plasma concentration of homocysteine (t-Hcy) is an important and independent risk factor for cardiovascular disease. Hypothyroidism is possibly also associated with an increased risk for coronary artery disease, which may be related to atherogenic changes in lipid profile. Because hypothyroidism decreases hepatic levels of enzymes involved in the remethylation pathway of homocysteine, we prospectively evaluated fasting and postload t-Hcy in patients before and after recovery of euthyroidism. Fasting and postload t-Hcy levels were higher in 40 patients with peripheral hypothyroidism (14 with autoimmune thyroiditis and 26 treated for thyroid cancer) in comparison with those of 26

controls (13.0 +/- 7.5 vs. 8.5 +/- 2.6 micromol/L, < .01, respectively, and 49.9 +/- 37.3 vs. 29.6 +/- 8.4 micromol/L < .001, respectively). On univariate analysis, fasting Hcy was positively related to thyrotropin (TSH) and inversely related to folates. Multivariate analysis confirmed TSH as the strongest predictor of t-Hcy independent of age, folate, vitamin B12, and creatinine. Thyroid hormone replacement significantly decreased fasting but not postload t-Hcy. We conclude that t-Hcy is elevated in hypothyroidism. The association of hyperhomocysteinemia and lipid abnormalities occurring in hypothyroidism may represent a dynamic atherogenic state. Thyroid hormone failed to completely normalize t-Hcy. Potential benefit of treatment with folic acid in combination with thyroid hormone replacement has to be tested given that hypothyroid patients were found to have lower levels of folate.

Selenium decreases thyroglobulin concentrations but does not affect the increased thyroxine-to-triiodothyronine ratio in children with congenital hypothyroidism.

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J Clin Endocrinol Metab 2001 Mar;86(3):1160-1163

Compared with euthyroid controls, patients with congenital hypothyroidism (CH) who are receiving L-T(4) treatment show elevated serum TSH relative to serum T(4) concentrations and increased T(4)/T(3) ratio. These abnormalities could be the consequence of impaired activity of the selenoenzymes deiodinases on which patients with CH rely to convert the ingested L-T(4) into active T(3). Eighteen patients (0.5-15.4 yr), diagnosed with CH in infancy, received selenomethionine (SeM, 20-60 microg selenium/day) for 3 months. The study took place in Belgium, a country where selenium intake is borderline. Compared with the values observed in age- and sex-matched euthyroid controls, patients with CH had decreased selenium, thyroglobulin and T(3) concentrations and increased TSH, reverse T(3), and T(4) concentrations and T(4)/T(3) ratio at baseline. Selenium supplementation caused a 74% increase in plasma selenium values but did not affect the activity of the selenoenzyme glutathione peroxidase used as a marker of selenium status. SeM abolished the TSH difference observed between CH patients and euthyroid controls at baseline and caused a significant decrease in thyroglobulin values. Thyroid hormone concentrations were not affected by SeM. In conclusion, our data suggest that selenium is not a limiting factor for peripheral T(4)-to-T(3) conversion in CH patients. In contrast, we find indirect evidence that SeM improves thyroid hormones feedback at the hypothalamo-pituitary level and decreases stimulation of the residual thyroid tissue, possibly suggesting greater intracellular T(4)-to-T(3) conversion.

Effects of selenium deficiency on thyroid necrosis, fibrosis and proliferation: a possible role in myxoedematous cretinism.

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Eur J Endocrinol 1995 Jul;133(1):99-109

It has been suggested that selenium deficiency is a co-factor to iodine deficiency in the pathogenesis of myxoedematous cretinism. The mechanism proposed is that the generation of hydrogen peroxide is greatly increased in iodine-deficient thyroid glands, and that selenium is involved in the control of hydrogen peroxide and its derived free radicals. This study was carried out to investigate the effect of the possibly impaired cellular defence mechanism associated with selenium deficiency on thyroid necrosis and tissue repair. For this purpose, we studied thyroid tissue from selenium- (SE-) and/or iodine-deficient (I-) rats before and after an acute toxic iodine overload. In thyroids, necrotic cells were numerous. Acute iodine administration increased this effect. Necrosis was associated with transient infiltration of inflammatory cells. In I-SE+ thyroids the tissue resumed its normal appearance. In I-SE- thyroid glands, the iodide toxicity was stronger, with greater necrosis and inflammatory reaction. The inflammation resolved but was replaced by fibrotic tissue. Fifteen days after the toxic overload, the connective tissue volume was twice the control value. Before iodide overload, the proportion of dividing cells was equal in I-SE+ and I-SE- thyroids. Three days after the iodide overload, this proportion was increased in I-SE+ thyroids but reduced in the I-SE- thyroids. Overall, the I-SE- thyroids had four times fewer dividing cells than the I-SE+ thyroids. In summary, selenium deficiency coupled to iodine deficiency increased necrosis, induced fibrosis and impeded compensatory epithelial cell proliferation. These results are compatible with histological and functional description of thyroid tissue from myxoedematous cretins.

Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism.

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Clin Endocrinol (Oxf). 2001 Feb;54(2):197-204.

OBJECTIVE: Hyperhomocysteinaemia is a risk factor for premature atherosclerotic vascular disease and venous thrombosis. The aim of the present study was to assess plasma total homocysteine (tHCys) concentrations in hypo- as well as hyperthyroid patients before and after treatment, and to evaluate the role of potential determinants of plasma tHCys levels in these patients.

DESIGN: Prospective follow up study.

PATIENTS: Fifty hypothyroid and 46 hyperthyroid patients were studied in the untreated state and again after restoration of euthyroidism.

MEASUREMENTS: Fasting plasma levels of tHCys and its putative determinants (plasma levels of free thyroxine (fT4), folate, vitamin B(12), renal function, sex, age, smoking status and the C677T polymorphism in the

methylenetetrahydrofolate reductase (MTHFR) gene were measured before and after treatment.

RESULTS: Restoration of the euthyroid state decreased both tHCys (17.6 +/- 10.2-13.0 +/- 4.7 micromol/l; < 0.005) and creatinine (83.9 +/- 22.0-69.8 +/- 14.2 micromol/l; <0.005) in hypothyroid patients and increased both tHCys (10.7 +/- 2.5-13.4 +/- 3.3 micromol/l; < 0.005) and creatinine (49.0 +/- 15.4-66.5 +/- 15.0 micromol/l; < 0.005) in hyperthyroid patients (values as mean +/- SD). Folate levels were lower in the hypothyroid group compared to the hyperthyroid group (11.7 +/- 6.4 and 15.1 +/- 7.6 nmol/l; < 0.05). Pretreatment tHCys levels correlated with log fT(4) (r = - 0.47), folate (r = - 0.21), plasma creatinine (r = 0.45) and age (r = 0.35) but not with C677T genotype. Multivariate analysis indicated that pretreatment log(fT(4)) levels and age accounted for 28% the variability of pre-treatment tHCys (tHCys = 14.2-5.50 log(fT(4)) + 0.14 age). After treatment the logarithm of the change (Delta) in fT(4) (expressed as the post-treatment fT(4)/pre-treatment fT(4) ratio) accounted for 45% of the variability in change of tHCys (tHCys = - 0.07-4.94 log (fT(4))); there was no independent contribution of changes in creatinine which was, however, strongly related to changes in tHCys (r = 0.61).

CONCLUSIONS: Plasma tHCys concentrations increased in hypothyroidism and decreased in hyperthyroidism. Plasma fT(4) is an independent determinant of tHCys concentrations. Lower folate levels and a lower creatinine clearance in hypo-thyroidism, and a higher creatinine clearance in hyperthyroidism only partially explain the changes in tHCys.

Anti-thyroid isoflavones from soybean: isolation, characterization, and mechanisms of action.

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Biochem Pharmacol 1997 Nov 15;54(10):1087-96

The soybean has been implicated in diet-induced goiter by many studies. The extensive consumption of soy products in infant formulas and in vegetarian diets makes it essential to define the goitrogenic potential. In this report, it was observed that an acidic methanolic extract of soybeans contains compounds that inhibit thyroid peroxidase- (TPO) catalyzed reactions essential to thyroid hormone synthesis. Analysis of the soybean extract using HPLC, UV-VIS spectrophotometry, and LC-MS led to identification of the isoflavones genistein and daidzein as major components by direct comparison with authentic standard reference isoflavones. HPLC fractionation and enzymatic assay of the soybean extract showed that the components responsible for inhibition of TPO-catalyzed reactions coeluted with daidzein and genistein. In the presence of iodide ion, genistein and daidzein blocked TPO-catalyzed tyrosine iodination by acting as alternate substrates, yielding mono-, di-, and triiodoisoflavones. Genistein also inhibited thyroxine synthesis using iodinated casein or human goiter thyroglobulin as substrates for the coupling reaction. Incubation of either

isoflavone with TPO in the presence of H2O2 caused irreversible inactivation of the enzyme; however, the presence of iodide ion in the incubations completely abolished the inactivation. The IC50 values for inhibition of TPO-catalyzed reactions by genistein and daidzein were ca. 1-10 microM, concentrations that approach the total isoflavone levels (ca. 1 microM) previously measured in plasma from humans consuming soy products. Because inhibition of thyroid hormone synthesis can induce goiter and thyroid neoplasia in rodents, delineation of anti-thyroid mechanisms for soy isoflavones may be important for extrapolating goitrogenic hazards identified in chronic rodent bioassays to humans consuming soy products.

Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism.

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Ann Intern Med. 1999 Sep 7;131(5):348-51.

BACKGROUND: Hyperhomocysteinemia is an independent risk factor for coronary, peripheral, and cerebrovascular disease. Elevated plasma homocysteine levels were described in a preliminary report on primary hypothyroidism.

OBJECTIVE: To determine whether restoration of euthyroidism by L-thyroxine replacement therapy would reduce or normalize plasma homocysteine levels.

DESIGN: Prospective cohort study.

SETTING: Outpatient endocrinology department of a tertiary center.

PATIENTS: 14 patients (10 women and 4 men; 25 to 77 years of age): 4 with newly diagnosed chronic (Hashimoto) hypothyroidism and 10 who had been rendered acutely hypothyroid (thyroid-stimulating hormone level < 25 mU/L) by total thyroidectomy for thyroid carcinoma.

MEASUREMENTS: Total plasma homocysteine levels were measured at baseline and 3 to 9 months later, after euthyroidism had been attained by L-thyroxine replacement therapy.

RESULTS: Median baseline plasma homocysteine levels in both sexes (women, 11.65 micromol/L [range, 7.2 to 26.5 micromol/L]; men, 15.1 micromol/L [range, 14.1 to 16.3 micromol/L]) were higher (P = 0.002) than those in healthy female (n = 35) and male (n = 36) volunteers (women, 7.52 micromol/L [range, 4.3 to 14.0 micromol/L]; men, 8.72 micromol/L [range, 5.94 to 14.98 micromol/L]). Eight patients (57%) had baseline plasma homocysteine levels that exceeded the upper limit of sex-specific reference ranges. Upon attainment of euthyroidism, all patients had a diminution in plasma homocysteine levels. The median overall change of -5.5 micromol/L (range, -15.4 to -1.8 micromol/L) corresponds to a

difference of -44% (range, -58% to -13%) (< 0.001). Homocysteine levels returned to normal in 7 of the 8 patients with elevated pretreatment values.

CONCLUSIONS: Hypothyroidism may be a treatable cause of hyperhomocysteinemia, and elevated plasma homocysteine levels may be an independent risk factor for the accelerated atherosclerosis seen in primary hypothyroidism.

Homocysteine and restenosis after percutaneous coronary intervention.

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J Med Assoc Thai. 2001 Dec;84 Suppl 3:S636-44.

Numerous clinical studies in Western and Asian countries suggest that individuals with elevated blood levels of homocysteine have an increased risk of atherosclerosis, myocardial infarction, cerebral infarction, and deep vein thrombosis. Homocysteine is also known to induce both atherogenic and thrombogenic mediators in cultured vascular cells so that homocysteine may influence the damage of endothelial cells, promote smooth muscle cell growth, induce atherogenic mediators and thrombus formation after coronary angioplasty. The association between homocysteine and restenosis after percutaneous coronary intervention (PCI) has been discussed. In this study, the relationship between plasma homocysteine levels and restenosis after PCI to investigate whether plasma homocysteine levels may be a predictor of restenosis after PCI was examined. One hundred consecutive patients who underwent successful PCI were enrolled and plasma homocysteine level was measured in all patients prior to PCI. Plasma for homocysteine level was obtained in 99 of 100 patients who had angioplasty. The mean plasma homocysteine concentration in the enrolled patients was 13.61 +/- 6.04 micromol/L. The minimum and maximum of plasma homocysteine were 4.40 micromol/L and 50.00 micromol/L, respectively. In healthy subjects, the normal reference range of homocysteine level is 5-15 micromol/L However, recent data suggest that some patients may be at increased cardiovascular and cerebrovascular risk at levels as low as 12 micromol/L. For this reason, both cut off points of homocysteine level < or = 15 micromol/L or < or = 12 micromol/L to identify the high homocysteine level group were used. Of 99 patients, high homocysteine level (< or = 15 micromol/L) was established in 9 patients with restenosis versus 20 patients without restenosis. If the cut off point of homocysteine level < or = 12 micromol/L was used, high homocysteine level was established in 14 patients with restenosis versus 39 patients without restenosis. From both cut off points of homocysteine level, there was no correlation between plasma homocysteine level and the restenosis group. (< 0.05).

Plasma total homocysteine levels in hyperthyroid and hypothyroid patients.

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Metabolism. 1998 Jan;47(1):89-93.

We found a higher plasma concentration of total homocysteine (tHcy), an independent risk factor for cardiovascular disease, in patients with hypothyroidism (mean, 16.3 micromol/L; 95% confidence interval [CI], 14.7 to 17.9 micromol/L) than in healthy controls (mean, 10.5 micromol/L; 95% CI, 10.1 to 10.9 micromol/L). The tHcy level of hyperthyroid patients did not differ significantly from that of the controls. Serum creatinine was higher in hypothyroid patients and lower in hyperthyroid patients than in controls, whereas serum folate was higher in hyperthyroid patients compared with the two other groups. In multivariate analysis, these differences did not explain the higher tHcy concentration in hypothyroidism. We confirmed the observation of elevated serum cholesterol in hypothyroidism, which together with the hyperhomocysteinemia may contribute to an accelerated atherogenesis in these patients.

Low selenium status in the elderly influences thyroid hormones.

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Clin Sci (Lond). 1995 Dec;89(6):637-42.

1. Iodothyronine 5'-deiodinase, which is mainly responsible for peripheral triiodothyronine (T3) production, has recently been demonstrated to be a selenium-containing enzyme. In the elderly, reduced peripheral conversion of thyroxine (T4) to T3 and overt hypothyroidism are frequently observed. 2. We measured serum selenium and erythrocyte glutathione peroxidase (as indices of selenium status), thyroid hormones and thyroid-stimulating hormone in 109 healthy euthyroid subjects (52 women, 57 men), carefully selected to exclude abnormally low thyroid hormone levels induced by acute or chronic diseases or calorie restriction. The subjects were subdivided into three age groups. To avoid conditions of under-nutrition or malnutrition, dietary records were obtained for a sample of 24 subjects, randomly selected and representative of the whole population for age and sex. 3. In order to properly assess the influence of selenium status on iodothyronine 5'-deiodinase type I activity, a double-blind placebo-controlled trial was also carried out on 36 elderly subjects, resident at a privately owned nursing home. 4. In the free-living population, a progressive reduction of the T3/T4 ratio (due to increased T4 levels) and of selenium and erythrocyte glutathione peroxidase activity was observed with advancing age. A highly significant linear correlation between T4, T3/T4 and selenium was observed in the population as a whole (for T4, $R = -0.312$, < 0.002; for T3/T4 ratio, $R = 0.32$, < 0.01) and in older subjects (for T4, $R = -0.40$, < 0.05; for T3/T4 ratio, $R = 0.54$, < 0.002). 5. The main result of the double-blind placebo-controlled trial was a significant improvement of selenium indices and a decrease

in the T4 level in selenium-treated subjects; serum selenium, erythrocyte glutathione peroxidase activity and thyroid hormones did not change in placebo-treated subjects. 6. We concluded that selenium status influences thyroid hormones in the elderly, mainly modulating T4 levels.

Selenium deficiency and hypothyroidism: a new etiology in the differential diagnosis of hypothyroidism in children.

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Biol Trace Elem Res 2000 Dec;77(3):199-208

Three female children presented with different clinical symptoms that could be related to impaired thyroid function. They underwent an accurate pediatric-endocrinologic diagnosis. Laboratory tests revealed no pathological findings, except latent hypothyroidism and selenium deficiency. Hypothyroidism was diagnosed by elevated basal TSH and by a pathological i.v.-TRH-stimulation test. After treating the children with sodium selenite orally for 4 wk, their metabolism had returned to normal and we saw a marked improvement of all clinical symptoms. For the first time, we have been able to describe hypothyroidism caused exclusively by selenium deficiency, the pathophysiology of which may be expressed as a malfunction of human 5'-deiodinases.

Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease.

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Circulation. 1995 Nov 15;92(10):2825-30.

BACKGROUND: High plasma homocysteine is associated with premature coronary artery disease in men, but the threshold concentration defining this risk and its importance in women and the elderly are unknown. Furthermore, although low B vitamin status increases homocysteine, the link between these vitamins and coronary disease is unclear.

METHODS AND RESULTS: We compared 304 patients with coronary disease with 231 control subjects. Risk factors and concentrations of plasma homocysteine, folate, vitamin B12, and pyridoxal 5'-phosphate were documented. A homocysteine concentration of 14 mumol/L conferred an odds ratio of coronary disease of 4.8 (< .001), and 5-mumol/L increments across the range of homocysteine conferred an odds ratio of 2.4 (< .001). Odds ratios of 3.5 in women and of 2.9 in those 65 years or older were seen (< .05). Homocysteine correlated negatively with all vitamins. Low pyridoxal 5'-phosphate (< 20 nmol/L) was seen in 10% of patients but in only 2% of control subjects (< .01), yielding an odds ratio of coronary disease adjusted for all risk factors, including high homocysteine, of 4.3 (< .05).

CONCLUSIONS: Within the range currently considered to be normal, the risk for coronary disease rises with increasing plasma homocysteine regardless of age and sex, with no threshold effect. In addition to a link with homocysteine, low pyridoxal-5'-phosphate confers an independent risk for coronary artery disease.

Serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and pregnenolone sulfate concentrations in patients with hyperthyroidism and hypothyroidism.

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Clin Chem. 2000 Apr;46(4):523-8.

BACKGROUND: Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) have been suggested to have protective effects against cardiovascular disease, cancer, immune-modulated diseases, and aging. We examined serum concentrations of DHEA, DHEA-S, and pregnenolone sulfate (PREG-S) in patients with thyroid dysfunction.

METHODS: Steroids extracted with methanol from serum sample were separated into an unconjugated fraction (DHEA) and a monosulfate fraction (DHEA-S and PREG-S), using a solid-phase extraction and an ion-exchange column. After separation of unconjugated steroids by HPLC, the DHEA concentration was measured by enzyme immunoassay. The monosulfate fraction was treated with arylsulfatase, and the freed steroids were separated by HPLC. The DHEA and PREG fractions were determined by gas chromatography-mass spectrometry, and the concentrations were converted into those of DHEA-S and PREG-S.

RESULTS: Serum concentrations of DHEA, DHEA-S, and PREG-S were all significantly lower in patients with hypothyroidism (n = 24) than in age- and sex-matched healthy controls (n = 43). By contrast, in patients with hyperthyroidism (n = 22), serum DHEA-S and PREG-S concentrations were significantly higher, but the serum DHEA concentration was within the reference interval. Serum concentrations of these three steroids correlated with serum concentrations of thyroid hormones in these patients. Serum albumin and sex hormone-binding globulin concentrations were not related to these changes in the concentration of steroids.

CONCLUSIONS: Serum concentrations of DHEA, DHEA-S, and PREG-S were decreased in hypothyroidism, whereas serum DHEA-S and PREG-S concentrations were increased but DHEA was normal in hyperthyroidism. Thyroid hormone may stimulate the synthesis of these steroids, and DHEA sulfotransferase might be increased in hyperthyroidism.