Osteoporosis
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ABSTRACTS

American Society for Bone and Mineral Research and The International Bone and Mineral Society. Second joint meeting of the American Society for Bone and Mineral Research and the International Bone and Mineral Society.

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S149-S708

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

Agnusdei D, Bufalino L.

*Calcif Tissue Int.* 1997; 61 Suppl 1:S23-S27.

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

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

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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, et al.

*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

Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures.

Anderson FH, Francis RM, Bishop JC, et al.

*Age Ageing.* 1997 Sep; 26(5):359-65.

OBJECTIVES: to investigate the effects of oral intermittent cyclical etidronate therapy on bone mineral density (BMD) in men with idiopathic vertebral osteoporosis. DESIGN: consecutive case series. SETTING: regional specialist clinic for metabolic bone disease. SUBJECTS: 42 men aged 35-81 (median 60.5) with established vertebral crush fractures and back pain, in whom secondary causes of osteoporosis had been excluded. INTERVENTION: repeated cycles of treatment with oral disodium etidronate 400 mg daily for 14 days followed by oral calcium 500 mg as citrate daily for 76 days. OUTCOME MEASURES: BMD measurement of the lumbar spine and femoral neck by dual energy x-ray absorptiometry at 6-12-month intervals; bone biochemistry (serum calcium, phosphate, alkaline phosphatase and urine calcium/creatinine and hydroxyproline/creatinine ratios) at 6-month intervals. RESULTS: all 42 men have been treated for more than 18 months, and 35 of them for more than 24 months. Median follow-up for the group as a whole is 31 months (range 18-45). The treatment was well tolerated. BMD at the lumbar spine increased by a mean of 0.024 g/cm2 per year of follow-up (95% confidence interval 0.017-0.032 g/cm2). This is equivalent to an average annual rate of change of 3.2% of baseline values. There was a small, non-significant rise in mean BMD at the hip equivalent to 0.7% of baseline values per year. Serum alkaline phosphatase tended to fall in the first 6 months of treatment, returning to baseline values at 2 years. Serum calcium and phosphate were unchanged and no decrease in urinary calcium/creatinine ratio or hydroxyproline/creatinine ratio was seen. CONCLUSIONS: intermittent cyclical etidronate therapy increased lumbar spine BMD over a 2-year period in an unselected group of men with osteoporotic vertebral fractures. This treatment warrants further evaluation in a randomized controlled trial

Beverage choices affect adequacy of children's nutrient intakes.

Ballew C, Kuester S, Gillespie C.

*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

The effectiveness of exercises on treatment of postmenopausal osteoporosis.

Belenoglu BUTTMGMME.

*Fiz Tedavi Rehabil Dergisi.* 1997; 21(1):20-4.

Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group.

Black DM, Cummings SR, Karpf DB, et al.

*Lancet.* 1996 Dec 7; 348(9041):1535-41.

BACKGROUND: Previous studies have shown that alendronate can increase bone mineral density (BMD) and prevent radiographically defined (morphometric) vertebral fractures. The Fracture Intervention Trial aimed to investigate the effect of alendronate on the risk of morphometric as well as clinically evident fractures in postmenopausal women with low bone mass. METHODS: Women aged 55-81 with low femoral-neck BMD were enrolled in two study groups based on presence or absence of an existing vertebral fracture. Results for women with at least one vertebral fracture at baseline are reported here. 2027 women were randomly assigned placebo (1005) or alendronate (1022) and followed up for 36 months. The dose of alendronate (initially 5 mg daily) was increased (to 10 mg daily) at 24 months, with maintenance of the double blind. Lateral spine radiography was done at baseline and at 24 and 36 months. New vertebral fractures, the primary endpoint, were defined by morphometry as a decrease of 20% (and at least 4 mm) in at least one vertebral height between the baseline and latest follow-up radiograph. Non-spine clinical fractures were confirmed by radiographic reports. New symptomatic vertebral fractures were based on self-report and confirmed by radiography. FINDINGS: Follow-up radiographs were obtained for 1946 women (98% of surviving participants). 78 (8.0%) of women in the alendronate group had one or more new morphometric vertebral fractures compared with 145 (15.0%) in the placebo group (relative risk 0.53 [95% Cl 0.41-0.68]). For clinically apparent vertebral fractures, the corresponding numbers were 23 (2.3%) alendronate and 50 (5.0%) placebo (relative hazard 0.45 [0.27-0.72]). The risk of any clinical fracture, the main secondary endpoint, was lower in the alendronate than in the placebo group (139 [13.6%] vs 183 [18.2%]; relative hazard 0.72 [0.58-0.90]). The relative hazards for hip fracture and wrist fracture for alendronate versus placebo were 0.49 (0.23-0.99) and 0.52 (0.31-0.87). There was no significant difference between the groups in numbers of adverse experiences, including upper-gastrointestinal disorders. INTERPRETATION: We conclude that among women with low bone mass and existing vertebral fractures, alendronate is well tolerated and substantially reduces the frequency of morphometric and clinical vertebral fractures, as well as other clinical fractures

Unregulated inflammation shortens human functional longevity.

Brod SA.

*Inflamm Res.* 2000 Nov; 49(11):561-70.

Systemic inflammation, represented in large part by the production of pro-inflammatory cytokines, is the response of humans to the assault of the non-self on the organism. Three distinct types of human ailments - namely autoimmunity, presenile dementia (Alzheimer's disease), or atherosclerosis - are initiated or worsened by systemic inflammation. Autoimmunity is unregulated hyperimmunity to organ-specific proteins, inducing rapid turnover of antigen-specific T cells of the acquired immune system with ultimate exhaustion and loss of acquired immunity IL-2 and IFN-gamma production and proliferative decline, conforming to the limited capacity of clonal division (Hayflick phenonmenon). In Alzheimer's disease (AD), the primary degenerative process of amyloid-beta (AJ3) protein precedes a cascade of events that ultimately leads to a local "brain inflammatory response". Unregulated systemic immune processes are secondary but important as a driving-force role in AD pathogenesis. Atherosclerosis, an underlying cause of myocardial infarction, stroke, and other cardiovascular diseases, consists of focal plaques characterized by cholesterol deposition, fibrosis, and inflammation. The presence of activated T lymphocytes and

macrophages indicate a local immunologic activation in the atherosclerotic plaque that may be secondary to unregulated pro-inflammatory cytokines too. The premature hyperimmunity of autoimmunity, the local "brain inflammatory response" to A/3 protein in AD, and the immune response to fatty changes in vessels in atherosclerosis all signal the critical importance of unregulated systemic inflammation to common neurological and cardiovascular disease that shortens the nominal longevity of humans

Nutrition and ulcerative colitis.

Burke A, Lichtenstein GR, Rombeau JL.

*Baillieres Clin Gastroenterol.* 1997 Mar; 11(1):153-74.

The role of diet in the aetiology and pathogenesis of ulcerative colitis (UC) remains uncertain. Impaired utilization by colonocytes of butyrate, a product of bacterial fermentation of dietary carbohydrates escaping digestion, may be important. Sulphur-fermenting bacteria may be involved in this impaired utilization. Oxidative stress probably mediates tissue injury but is probably not of causative importance. Patients with UC are prone to malnutrition and its detrimental effects. However, there is no role for total parenteral nutrition and bowel rest as primary therapy for UC. The maintenance of adequate nutrition is very important, particularly in the peri-operative patient. In the absence of massive bleeding, perforation, toxic megacolon or obstruction, enteral rather than parenteral nutrition should be the mode of choice. Nutrients may be beneficial as adjuvant therapy. Butyrate enemas have improved patients with otherwise recalcitrant distal colitis in small studies. Non-cellulose fibre supplements are of benefit in rats with experimental colitis. Eicosapentaenoic acid in fish oil has a steroid-sparing effect which, although modest, is important, particularly in terms of reducing the risk of osteoporosis, but it seems to have no role in the patient with inactive disease. gamma-Linolenic acid and anti-oxidants also are showing promise. Nutrients may also modify the increased risk of colorectal carcinoma. Oxidative stress can damage tissue DNA but there are no data published at present on possible protection from oral anti-oxidants. Butyrate protects against experimental carcinogenesis in rats with experimental colitis. Folate supplementation is weakly associated with decreased incidence of cancer in UC patients when assessed retrospectively. Vigilance should be maintained for increased micronutrient requirements and supplements given as appropriate. Calcium and low-dose vitamin D should be given to patients on long-term steroids and folate to those on sulphasalazine

Management of osteoporosis. An overview.

Castelo-Branco C.

*Drugs Aging.* 1998; 12 Suppl 1:25-32.

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 the rate of bone loss 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

The different routes of administration and the effect of hormone replacement therapy on osteoporosis.

Christiansen C.

*Fertil Steril.* 1994 Dec; 62(6 Suppl 2):152S-6S.

OBJECTIVE: To review osteoporosis, a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to increased bone fragility and a consequent increase in fracture risk. The disorder has become a major health problem in the West, where increased life expectancy has placed new emphasis on disorders related to aging. DESIGN: Review of selected literature. MAIN OUTCOME MEASURES: Bone mass increases rapidly in growing children and adolescents, reaching a peak in adults in their 20s and 30s. After 35 to 45 years of age, bone mass begins to decline slowly. Men lose bone mass at approximately the same rate over their lifetime; in women, however, the rate of bone loss increases dramatically after their

menopause, whether it is natural or surgical. It is also important to note that bone mass in women below the age of 50 is just two thirds of that found in men. These two factors--the low initial adult bone mass and the more rapid bone loss--combine to produce a high incidence of osteoporosis in elderly women. Significant morbidity and mortality are attributed to osteoporosis-related fractures, underlining the importance of new therapeutic and preventive modalities being evaluated and applied in high-risk populations. In adult women before the onset of menopause, rates of bone formation and bone resorption are approximately equal; calcium balance is maintained, and no loss of bone mass occurs. But after menopause, although both bone formation and bone resorption rates increase, the rate of bone resorption increase more rapidly, resulting in calcium imbalance and a net loss of bone. The first goal of therapy for osteoporosis is thus the restoration of bone resorption and bone formation to premenopausal levels. Optimally, bone formation may be maintained at a slightly higher level than that of bone resorption, producing a positive calcium balance

Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study.

Colditz GA, Rosner B.

*Am J Epidemiol.* 2000 Nov 15; 152(10):950-64.

Because of the temporal relations between reproductive risk factors and incidence of breast cancer, the authors developed a nonlinear Poisson regression that accounts for time and summarizes risk to age 70 years. Reproductive risk factors, benign breast disease, use of postmenopausal hormones, weight, and alcohol intake were evaluated as risk factors. Among 58,520 women aged 30-55 years in 1980, followed through June 1, 1994, 1,761 incident invasive breast cancer cases were identified. All risks are multivariate adjusted. History of benign breast disease is associated with a 57% increase (95% confidence interval (CI): 43%, 73%) in cumulative risk of breast cancer by age 70 years. Use of unopposed postmenopausal estrogen from ages 50-60 years increases risk of breast cancer to age 70 by 23% (95% CI: 6%, 42%) compared with a woman who never uses hormones. Ten years of use of estrogen plus progestin increases risk to age 70 years by 67% (95% CI: 18%, 136%). Compared with never drinking alcohol, one drink per day from age 18 years increases risk to age 70 by 7% (95% CI: 0%, 13%). Use of unopposed postmenopausal hormones for 10 years significantly increases the risk of breast cancer, and the addition of progestin further increases the risk

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

Craciun AM, Wolf J, Knapen MH, et al.

*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

Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial.

Cummings SR, Black DM, Thompson DE, et al.

*JAMA.* 1998 Dec 23; 280(24):2077-82.

CONTEXT: Alendronate sodium reduces fracture risk in postmenopausal women who have vertebral fractures, but its effects on fracture risk have not been studied for women without vertebral fractures. OBJECTIVE: To test the hypothesis that 4 years of alendronate would decrease the risk of clinical and vertebral fractures in women who have low bone mineral density (BMD) but no vertebral fractures. DESIGN: Randomized, blinded, placebo-controlled trial. SETTING: Eleven community-based clinical research centers. SUBJECTS: Women aged 54 to 81 years with a femoral neck BMD of 0.68 g/cm2 or less (Hologic Inc, Waltham, Mass) but no vertebral fracture; 4432 were randomized to alendronate or placebo and 4272 (96%) completed outcome measurements at the final visit (an average of 4.2 years later). INTERVENTION: All participants reporting calcium intakes of 1000 mg/d or less received a supplement containing 500 mg of calcium and 250 IU of cholecalciferol. Subjects were randomly

assigned to either placebo or 5 mg/d of alendronate sodium for 2 years followed by 10 mg/d for the remainder of the trial. MAIN OUTCOME MEASURES: Clinical fractures confirmed by x-ray reports, new vertebral deformities detected by morphometric measurements on radiographs, and BMD measured by dual x-ray absorptiometry. RESULTS: Alendronate increased BMD at all sites studied (P2.5 SDs below the normal young adult mean; RH, 0.64; 95% CI, 0.50-0.82; treatment-control difference, 6.5%; number needed to treat [NNT], 15), but there was no significant reduction among those with higher BMD (RH, 1.08; 95% CI, 0.87-1.35). Alendronate decreased the risk of radiographic vertebral fractures by 44% overall (relative risk, 0.56; 95% CI, 0.39-0.80; treatment-control difference, 1.7%; NNT, 60). Alendronate did not increase the risk of gastrointestinal or other adverse effects. CONCLUSIONS: In women with low BMD but without vertebral fractures, 4 years of alendronate safely increased BMD and decreased the risk of first vertebral deformity. Alendronate significantly reduced the risk of clinical fractures among women with osteoporosis but not among women with higher BMD

Treatment of metastatic bone disease in breast cancer: bisphosphonates.

Diel IJ, Solomayer EF, Bastert G.

*Clin Breast Cancer.* 2000 Apr; 1(1):43-51.

Like other metastases, bone metastases in breast cancer patients are not only a sign of the incurable nature of the underlying disease, but are also associated with specific complications. In particular, bone pain and pathological fractures impair the quality of life of those affected. Any treatment concept must, therefore, place the highest priority on preventing or reducing skeletal complications. There are two treatment options--local and systemic. Local therapy includes radiotherapy as well as surgical and orthopedic measures. The four pillars of systemic treatment are hormone therapy, chemotherapy, antiresorptive therapy with bisphosphonates, and treatment with centrally and/or peripherally acting analgesics. A precondition for successful treatment is close cooperation between medical/clinical oncologists, radiotherapists, surgeons/orthopedists, gynecologists, pain specialists, and endocrinologists (in the presence of a hypercalcemic syndrome). Patients with breast cancer associated solely with osseous metastasis may live for a number of years. It is, therefore, all the more important to start appropriate therapeutic measures early. Bisphosphonates play a particularly valuable role, since their main effect lies in the prevention of skeletal complications. Rather than replacing antineoplastic therapy, this class of substances supplements other treatments. Once started, bisphosphonate therapy should be given for the remainder of the patient's life, even in the event of osseous progression

Magnesium status and health.

Dreosti IE.

*Nutr Rev.* 1995 Sep; 53(9 Pt 2):S23-S27.

Bisphosphonates modulate the effect of macrophage-like cells on osteoblast.

Evans CE.

*Int J Biochem Cell Biol.* 2002 May; 34(5):554-63.

Macrophages (MPs) are present in many tissues and have been implicated in the excessive bone resorption seen in patients with skeletal disorders. Our previous studies showed that macrophage-like cells influenced osteoblasts (OB) in co-culture, as number and activity of osteoblasts were decreased in co-cultures compared with controls. Macrophages are probable precursors of osteoblasts which have been shown to be inhibited by bisphosphonates (BPs). Bisphosphonates also modulate macrophage and osteoblasts activity. This study investigated whether addition of bisphosphonates to co-cultures of osteoblast and macrophages could reduce or block the adverse effects of macrophages on osteoblasts. The results showed that, compared to controls, fewer osteoblasts were present over time in macrophage/osteoblast co-cultures (at day 12, 15.5 x 10(4) and 8.8 x 10 (4); P<0.0001) and that addition of bisphosphonates (10(-9)-10(-5)M) to the co-cultures prevented this reduction (P<0.001). Bisphosphonates also elicited an increase in numbers of osteoblast (82%) and restored alkaline phosphatase (ALP) activity, which was reduced by 15% (P approximately equal to 0.05) compared to control levels. The number of macrophages in co-cultures was reduced when bisphosphonates were added (P<0.001) and release of lactate dehydrogenase (LDH) was seen, which was not detectable in control cultures. It therefore, appears that bisphosphonates initiated macrophage death. These results demonstrated that the inhibitory effect of macrophages on osteoblasts in vitro could be overcome by the action of bisphosphonates. These findings have implications for the treatment of skeletal conditions where macrophage-derived cytokines are important, such as arthritis and implant loosening, although it is clearly important to distinguish between those bisphosphonates which enhance synthesis of pro-inflammatory cytokines and those which inhibit such synthesis

Protein consumption and bone fractures in women.

Feskanich D, Willett WC, Stampfer MJ, et al.

*Am J Epidemiol.* 1996 Mar 1; 143(5):472-9.

Dietary protein increases urinary calcium losses and has been associated with higher rates of hip fracture in cross-cultural studies. However, the relation between protein and risk of osteoporotic bone fractures among individuals has not been examined in detail. In this prospective study, usual dietary intake was measured in 1980 in a cohort of 85,900 women, aged 35-59 years, who were participants in the Nurses' Health Study. A mailed food frequency questionnaire was used and incident hip (n = 234) and distal forearm (n = 1,628) fractures were identified by self-report during the following 12 years. Information on other factors related to osteoporosis, including obesity, use of postmenopausal estrogen, smoking, and physical activity, was collected on biennial questionnaires. Dietary measures were updated in 1984 and 1986. Protein was associated with an increased risk of forearm fracture (relative risk (RR) = 1.22, 95% confidence interval (Cl) 1.04-1.43, p for trend = 0.01) for women who consumed more than 95 g per day compared with those who consumed less than 68 g per day. A similar increase in risk was observed for animal protein, but no association was found for consumption of vegetable protein. Women who consumed five or more servings of red meat per week also had a significantly increased risk of forearm fracture (RR = 1.23, 95% Cl 1.01-1.50) compared with women who ate red meat less than once per week. Recall of teenage diet did not reveal any increased risk of forearm fracture for women with higher consumption of animal protein or red meat during this earlier period of life. No association was observed between adult protein intake and the incidence of hip fractures, though power to assess this association was low

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

Feskanich D, Weber P, Willett WC, et al.

*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

Bisphosphonates: preclinical aspects and use in osteoporosis.

Fleisch HA.

*Ann Med.* 1997 Feb; 29(1):55-62.

The bisphosphonates are synthetic compounds characterized by a P-C-P bond. They have a strong affinity to calcium phosphates and hence to bone mineral. In vitro they inhibit both formation and dissolution of the latter. Many of the bisphosphonates inhibit bone resorption, the newest compounds being 10,000 times more active than etidronate, the first bisphosphonate described. The antiresorbing effect is cell mediated, partly by a direct action on the osteoclasts, partly through the osteoblasts, which produce an inhibitor of osteoclastic recruitment. When given in large amounts, some bisphosphonates can also inhibit normal and ectopic mineralization through a physical-chemical inhibition of crystal growth. In the growing rat the inhibition of resorption is accompanied by an increase in intestinal absorption and an increased balance of calcium. Bisphosphonates also prevent various types of experimental osteoporosis, such as after immobilization, ovariectomy, orchidectomy, administration of corticosteroids, or low calcium diet. The P-C-P bond of the bisphosphonates is completely resistant to enzymatic hydrolysis. The bisphosphonates studied up to now, such as etidronate, clodronate, pamidronate, and alendronate, are absorbed, stored, and excreted unaltered. The intestinal absorption of the bisphosphonates is low, between 1% or less and 10% of the amount ingested. The newer bisphosphonates are at the lower end of the scale. The absorption diminishes when the compounds are given with food, especially in the presence of calcium. Bisphosphonates are rapidly cleared from plasma, 20%-80% being deposited in bone and the remainder excreted in the urine. In bone, they deposit at sites of mineralization as well as under the osteoclasts. In contrast to plasma, the half-life in bone is very long, partially as long as the half-life of the bone in which they are deposited. In humans, bisphosphonates are used successfully in diseases with increased

bone turnover, such as Paget's disease, tumoural bone disease, as well as in osteoporosis. Various bisphosphonates, such as alendronate, clodronate, etidronate, ibandronate, pamidronate, and tiludronate, have been investigated in osteoporosis. All inhibit bone loss in postmenopausal women and increase bone mass. Furthermore, bisphosphonates are also effective in preventing bone loss both in corticosteroid-treated and in immobilized patients. The effect on the rate of fractures has recently been proven for alendronate. In humans, the adverse effects depend upon the compound and the amount given. For etidronate, practically the only adverse effect is an inhibition of mineralization. The aminoderivatives induce for a period of 2-3 days a syndrome with pyrexia, which shows a similitude with an acute phase reaction. The more potent compounds can induce gastrointestinal disturbances, sometimes oesophagitis, when given orally. Bisphosphonates are an important addition to the therapeutic possibilities in the prevention and treatment of osteoporosis

Clinical use of selective estrogen receptor modulators.

Fontana A, Delmas PD.

*Curr Opin Rheumatol.* 2001 Jul; 13(4):333-9.

The concept of selective estrogen receptor modulators (SERMs) is derived from the observation that tamoxifen, an effective adjuvant therapy of breast cancer that has an antiestrogenic effect on breast tissue, has estrogen-like effects on the skeleton and on plasma lipoproteins. Raloxifene is a SERM that has undergone extensive clinical investigation in the prevention and treatment of postmenopausal osteoporosis. It prevents bone loss at all skeletal sites, and in a large trial in osteoporotic women, the incidence of vertebral fractures was significantly decreased (relative risk 0.64) after up to 4 years of treatment with raloxifene 60 mg. The decrease of nonvertebral fractures did not reach the level of significance. Raloxifene decreased significantly the incidence of breast cancer (relative risk 0.28) and has no effect on the risk of endometrial cancer. SERMs are likely to play an important role in the management of postmenopausal women

Analgesic effect of intravenous pamidronate on chronic back pain due to osteoporotic vertebral fractures.

Gangji V, Appelboom T.

*Clin Rheumatol.* 1999; 18(3):266-7.

Pamidronate, a bisphosphonate analogue has been evaluated in a retrospective study for its analgesic effect on chronic back pain due to vertebral fractures in 26 patients suffering from senile osteoporosis or glucocorticoid-induced osteoporosis. Sixty milligrams of pamidronate was administered intravenously every 3 months for one year. After three months of treatment, the pain score fell from 3.2 +/- 0.1 to 1.2 +/- 0.2 in both groups. In conclusion, intravenous pamidronate seems to be a valuable treatment for chronic back pain due to osteoporotic vertebral fractures

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

Gennari C, Agnusdei D, Crepaldi G, et al.

*Menopause.* 1998; 5(1):9-15.

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

Bisphosphonates: safety and efficacy in the treatment and prevention of osteoporosis.

Greenspan SL, Harris ST, Bone H, et al.

*Am Fam Physician.* 2000 May 1; 61(9):2731-6.

Osteoporosis affects more than 28 million Americans. With the advent of accessible and affordable diagnostic studies,

awareness and recognition of this disease by patients and clinicians are growing. Osteoporotic fractures of the spine and hip are costly and associated with significant morbidity and mortality. Over the past decade, a surge of new antiosteoporotic drugs have been labeled or are awaiting labeling by the U.S. Food and Drug Administration. One class of agents used to treat osteoporosis is the bisphosphonates, which inhibit bone resorption, cause an increase in bone mineral density and reduce the risk of future fractures caused by aging, estrogen deficiency and corticosteroid use. Overall, bisphosphonates have been shown to have a strong safety and tolerability profile

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

Haden ST, Glowacki J, Hurwitz S, et al.

*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

Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease.

Haderslev KV, Tjellesen L, Sorensen HA, et al.

*Gastroenterology.* 2000 Sep; 119(3):639-46.

BACKGROUND & AIMS: Low bone mineral density (BMD) is a common complication of Crohn's disease and may lead to increased morbidity and mortality because of fractures. We investigated the effect of treatment with the bisphosphonate alendronate on bone mass and markers of bone remodeling in patients with Crohn's disease. METHODS: A 12-month double-blind, randomized, placebo-controlled trial examined the effect of a 10-mg daily dose of alendronate. Thirty-two patients with a bone mass T score of -1 of the hip or lumbar spine were studied. The main outcome measure was the difference in the mean percent change in BMD of the lumbar spine measured by dual-energy x-ray absorptiometry. Secondary outcome measures included changes in BMD of the hip and total body and biochemical markers of bone turnover (S-osteocalcin, urine pyridinoline, and urine deoxypyridinoline excretion). RESULTS: Mean (+/-SEM) BMD of the lumbar spine showed an increase of 4.6% +/- 1.2% in the alendronate group compared with a decrease of 0.9% +/- 1.0% in patients receiving placebo (P < 0.01). BMD of the hip increased by 3.3% +/- 1.5% in the alendronate group compared with a smaller increase of 0.7% +/- 1.1% in the placebo group (P = "0.08)." Biochemical markers of bone turnover decreased significantly in the alendronate group (P < 0.001). Alendronate was well tolerated, and there was no difference in adverse events among treatment groups. CONCLUSIONS: Treatment with alendronate, 10 mg daily, significantly increased BMD in patients with Crohn's disease and was safe and well tolerated

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

Halpner AD, Kellermann G, Ahlgrimm MJ, et al.

*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

Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group.

Harris ST, Watts NB, Genant HK, et al.

*JAMA.* 1999 Oct 13; 282(14):1344-52.

CONTEXT: Risedronate, a potent bisphosphonate, has been shown to be effective in the treatment of Paget disease of bone and other metabolic bone diseases but, to our knowledge, it has not been evaluated in the treatment of established postmenopausal osteoporosis. OBJECTIVE: To test the efficacy and safety of daily treatment with risedronate to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial of 2458 ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline who were enrolled at 1 of 110 centers in North America conducted between December 1993 and January 1998. INTERVENTIONS: Subjects were randomly assigned to receive oral treatment for 3 years with risedronate (2.5 or 5 mg/d) or placebo. All subjects received calcium, 1000 mg/d. Vitamin D (cholecalciferol, up to 500 IU/d) was provided if baseline levels of 25-hydroxyvitamin D were low. MAIN OUTCOME MEASURES: Incidence of new vertebral fractures as detected by quantitative and semiquantitative assessments of radiographs; incidence of radiographically confirmed nonvertebral fractures and change from baseline in bone mineral density as determined by dual x-ray absorptiometry. RESULTS: The 2.5 mg/d of risedronate arm was discontinued after 1 year; in the placebo and 5 mg/d of risedronate arms, 450 and 489 subjects, respectively, completed all 3 years of the trial. Treatment with 5 mg/d of risedronate, compared with placebo, decreased the cumulative incidence of new vertebral fractures by 41 % (95% confidence interval [CI], 18%-58%) over 3 years (11.3 % vs 16.3%; P= .003). A fracture reduction of 65% (95% CI, 38%-81 %) was observed after the first year (2.4% vs 6.4%; P<.001). The cumulative incidence of nonvertebral fractures over 3 years was reduced by 39% (95% CI, 6%-61 %) (5.2 % vs 8.4%; P = ".02)." Bone mineral density increased significantly compared with placebo at the lumbar spine (5.4% vs 1.1 %), femoral neck (1.6% vs -1.2%), femoral trochanter (3.3% vs -0.7%), and midshaft of the radius (0.2% vs -1.4%). Bone formed during risedronate treatment was histologically normal. The overall safety profile of risedronate, including gastrointestinal safety, was similar to that of placebo. CONCLUSIONS: These data suggest that risedronate therapy is effective and well tolerated in the treatment of women with established postmenopausal osteoporosis

Effect of etidronate treatment on bone mass of male nephrolithiasis patients with idiopathic hypercalciuria and osteopenia.

Heilberg IP, Martini LA, Teixeira SH, et al.

*Nephron.* 1998 Aug; 79(4):430-7.

Osteopenia is frequently found among calcium stone forming (CSF) patients with hypercalciuria. We investigated the effect of a 2-year therapeutic course of etidronate, a bone-sparing agent, in 7 young male CSF patients. The treatment consisted of a cyclic intermittent administration of phosphate followed by sodium etidronate and calcium supplementation every 74 days. Bone mineral density (BMD) measured at 12-month intervals and bone biopsies performed at baseline and after 2 years were the primary efficacy parameters. Mean lumbar spine BMD increased significantly after the 1st year by 2.6 +/- 1.0% (mean +/- SE, $p < 0.05$) and nonsignificantly after the 2nd year by 5.6 +/- 2.6%. Nonsignificant changes were observed for femoral neck mean BMD after either the 1st or the 2nd year (decrease of 2.0 +/- 1.0% and 2.0 +/- 3.0%, respectively). Mean histomorphometric parameters showed that bone volume, osteoid volume, and eroded surfaces did not differ from baseline (13.9 +/- 2.2 vs. 12.2 +/- 1.1%, 1.2 +/- 0.7 vs. 2.6 +/- 0.7%, and 20.7 +/- 6.2 vs. 13. 7 +/- 1.3%, respectively). Osteoid surface was significantly lower than baseline values (9.5 +/- 5.2 vs. 18.8 +/- 5.3%, $p < 0.05$). These data suggest that etidronate given to young male CSF patients presenting with hypercalciuria and osteopenia led to a significant amelioration of BMD, evident only in the lumbar spine after 1 year of treatment. There was no histological evidence of long-term improvement in bone remodeling

Depressed levels of circulating menaquinones in patients with osteoporotic fractures of the spine and femoral neck.

Hodges SJ, Pilkington MJ, Stamp TC, et al.

*Bone.* 1991; 12(6):387-9.

Vitamin K1 functions in the conversion of glutamate residues, present in certain bone peptides, into the putatively active gamma-carboxyglutamate form. We have shown previously that the circulating levels of vitamin K1 are depressed in osteoporotic patients. However, it is known that menaquinones (vitamin K2:MK) may be more effective than vitamin K1 in this conversion of the inactive to active form of glutamate residues. A procedure for measuring such menaquinones has now demonstrated a

marked deficiency of MK-7 and MK-8 in patients with osteoporotic fractures. It is suggested that estimates of circulating levels of K1, MK-7, and MK-8 might provide a biochemical risk marker of osteoporotic fractures

Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group.

Hosking D, Chilvers CE, Christiansen C, et al.

*N Engl J Med.* 1998 Feb 19; 338(8):485-92.

BACKGROUND: Estrogen-replacement therapy prevents osteoporosis in postmenopausal women by inhibiting bone resorption, but the balance between its long-term risks and benefits remains unclear. Whether other antiresorptive therapies can prevent osteoporosis in these women is also not clear. METHODS: We studied the effect of 2.5 mg or 5 mg of alendronate per day or placebo on bone mineral density in 1174 postmenopausal women under 60 years of age. An additional 435 women who were prepared to receive a combination of estrogen and progestin were randomly assigned to one of the above treatments or open-label estrogen-progestin. The main outcome measure was the change in bone mineral density of the lumbar spine, hip, distal forearm, and total body measured annually for two years by dual-energy x-ray absorptiometry. RESULTS: The women who received placebo lost bone mineral density at all measured sites, whereas the women treated with 5 mg of alendronate daily had a mean (+/-SE) increase in bone mineral density of 3.5+/-0.2 percent at the lumbar spine, 1.9+/-0.1 percent at the hip, and 0.7+/-0.1 percent for the total body (all $P<0.001$). Women treated with 2.5 mg of alendronate daily had smaller increases in bone mineral density. Alendronate did not increase bone mineral density of the forearm, but it slowed the loss. The responses to estrogen-progestin were 1 to 2 percentage points greater than those to the 5-mg dose of alendronate. Alendronate was well tolerated, with a safety profile similar to that of placebo or estrogen-progestin. CONCLUSIONS: Alendronate prevents bone loss in postmenopausal women under 60 years of age to nearly the same extent as estrogen-progestin

Osteoporosis: epidemiology, diagnosis, and treatment.

Iqbal MM.

*South Med J.* 2000 Jan; 93(1):2-18.

Osteoporosis is an important health problem in the United States affecting approximately 24 million Americans, 15 to 20 million of whom are women over 45 years of age. Bone fractures are the major cause of morbidity and mortality associated with osteoporosis. The most common fractures are those of the forearm, hip, and vertebral body, as well as the humerus, tibia, pelvis, and ribs. Osteoporosis-related injuries result in complications leading to prolonged hospitalization, decreased independence, increased incidence of depression, and a reduced quality of life. The disease takes an enormous personal and economic toll, with estimated costs in excess of $13.8 billion annually for direct medical treatment. The incidence of osteoporosis-related fractures is increasing and constitutes a major public health problem in the United States. With a few preventive measures such as identification of risk factors, careful examination, and a few simple diagnostic tests, prevention of osteoporosis during the teen and early adult years is far superior to any treatment for older individuals. Osteoporosis can be identified and an appropriate treatment strategy can be determined

IL-6, DHEA and the ageing process.

James K, Premchand N, Skibinska A, et al.

*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.

*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

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

Man Z, Otero AB.

*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

Experimental and clinical pharmacology: bisphosphonates-mechanisms of action.

Martin TJG, V.

*Aust Prescriber.* 2000; 23(6):130-2.

[Osteoporosis - Evidence based therapy].

Minne HW, Begerow B, Pfeifer M.

*Z Gastroenterol.* 2002 Apr; 40 Suppl 1:S57-S61.

Osteoporosis therapy has been controversially discussed in the past. In the meantime, several therapeutic options to prevent fractures are available for this disease. With respect to proven fracture benefit, however, the quality of evidence from randomised and controlled clinical trials varies substantially among therapies. From systematic research the best external evidence is available for a supplementation with calcium and vitamin D and a therapy with the bisphosphonates alendronate or risedronate, as well as the SERM raloxifene. For other therapeutic agents like fluorides, vitamin D metabolites, calcitonin and etidronate the

quality of evidence is much lower. So far, there is no evidence for other pharmaceutical therapies. Hip protectors are effective in the prevention of hip fractures

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

Nozaki M, Hashimoto K, Inoue Y, et al.

*Int J Gynaecol Obstet.* 1998 Jul; 62(1):69-75.

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

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

Potter SM, Baum JA, Teng H, et al.

*Am J Clin Nutr.* 1998 Dec; 68(6 Suppl):1375S-9S.

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.

Experimental, epidemiological, and clinical data indicate that progesterone is active in bone metabolism. Progesterone appears to act directly on bone by engaging an osteoblast receptor or indirectly through competition for a glucocorticoid osteoblast receptor. Progesterone seems to promote bone formation and/or increase bone turnover. It is possible, through estrogen-stimulated increased progesterone binding to the osteoblast receptor, that progesterone plays a role in the coupling of bone resorption with bone formation. A model of the interdependent actions of progesterone and estrogen on appropriately-"ready" cells in each bone multicellular unit can be tied into the integrated secretions of these hormones within the ovulatory cycle. Figure 5 is an illustration of this concept. It shows the phases of the bone remodeling cycle in parallel with temporal changes in gonadal steroids across a stylized ovulatory cycle. Increasing estrogen production before ovulation may reverse the resorption occurring in a "sensitive" bone multicellular unit while gonadal steroid levels are low at the time of menstrual flow. The bone remodeling unit would then be ready to begin a phase of formation as progesterone levels peaked in the midluteal phase. From this perspective, the normal ovulatory cycle looks like a natural bone-activating, coherence cycle. 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."

Cyclic medroxyprogesterone treatment increases bone density: a controlled trial in active women with menstrual cycle disturbances.

Prior JC, Vigna YM, Barr SI, et al.

*Am J Med.* 1994 Jun; 96(6):521-30.

OBJECTIVE: Bone loss occurs in young women who experience amenorrhea or ovulatory disturbances. The purpose of this study was to determine whether bone loss could be prevented by simulating a more normal hormonal pattern, using treatment with cyclic medroxyprogesterone, with or without calcium supplementation, in physically active women with disturbed menstruation. DESIGN: This study was a 1-year randomized, double-blind, placebo-controlled trial. Women who were stratified by menstrual cycle disturbance were randomized into four groups. The outcome variable was the change in spinal bone density measured by dual energy techniques. SETTING: A large metropolitan area. PARTICIPANTS: Sixty-one healthy, normal-weight physically active premenopausal women aged 21 to 45 years who experienced amenorrhea, oligomenorrhea, anovulation, or short luteal phase cycles completed the study. INTERVENTION: Therapies were cyclic medroxyprogesterone (10 mg/day for 10 days per month) and calcium carbonate (1,000 mg/day of calcium) in four groups: (A) (n = 16) cyclic medroxyprogesterone plus calcium carbonate; (B) (n = 16) cyclic medroxyprogesterone with calcium placebo; (C) (n = 15) placebo medroxyprogesterone with active calcium; or (D) (n = 14) both medroxyprogesterone and calcium placebos. RESULTS: The initial bone density (mean = 1.12 g/cm2) did not differ by group (P = 0.85). The 1-year bone density change was strongly related to treatment with medroxyprogesterone (P = 0.0001) and weakly to calcium (P = 0.072) treatment. Bone density increased significantly (+1.7% +/- 0.5%, +/- SEM, P = 0.004) in the medroxyprogesterone-treated groups (A and B), did not change in the calcium-treated group (C) (-0.7% +/- 0.6%, P = 0.28), and decreased on both placebos (D) (-2.0% +/- 0.6%, P = 0.005). CONCLUSIONS: Cyclic medroxyprogesterone increased spinal bone density in physically active women experiencing amenorrhea or ovulatory disturbances. POTENTIAL CLINICAL SIGNIFICANCE: Amenorrhea, oligomenorrhea, anovulation, and short luteal phase cycles are common in premenopausal women and associated with spinal bone loss occurring at a stage of life when bone density would normally be stable or increasing. This controlled trial shows a significant gain in bone in women in the cyclic medroxyprogesterone intervention group, whereas those subjects in the placebo group lost bone. Calcium supplementation appeared to be helpful but did not reach statistical significance. The implications of these findings for the prevention of osteoporosis warrant further investigation

Bisphosphonates for prevention of postmenopausal osteoporosis.

Ravn P.

*Dan Med Bull.* 2002 Feb; 49(1):1-18.

Our studies showed that 5 mg alendronate per day was the lowest, most effective dose that persistently prevented bone loss in recently postmenopausal women with normal bone mass. The effect on bone mass and biochemical markers was found comparable to that of commonly recommended regimens of postmenopausal HRT, and 5 mg alendronate per day is suggested as a new option for prevention of postmenopausal osteoporosis. HRT must, however, still be considered the first choice for this indication because of additional beneficial effects on other organ systems. The effect of alendronate was unaffected by bone or fat mass status, but increased with increasing postmenopausal age. The implications were that alendronate stabilized bone mass to a comparable extent in women at particular risk of osteoporosis because of thin body habitus or low bone mass and in healthy postmenopausal women with normal bone mass. Calcium supplementation was insufficient to prevent bone loss and did not add an effect on bone metabolism when combined with alendronate treatment in recently postmenopausal women. The gastrointestinal risk and adverse event profile of 5 mg alendronate per day was comparable to that of placebo, and this dose of alendronate appeared safe for long-term use. Bone loss resumed at a normal postmenopausal rate promptly after withdrawal of alendronate in early postmenopausal women consistent with a substantial underlying natural bone loss during early menopause. Oral ibandronate increased bone mass at all skeletal regions in elderly postmenopausal women with low bone mass, and 2.5 mg ibandronate per day was the lowest dose with this effect. The results are indicative of ibandronate as an option for secondary prevention of postmenopausal osteoporosis, but longer-term phase III trials should be performed before ibandronate can be recommended for this indication. The study showed that 2.5 mg ibandronate per day was efficient for prevention of bone loss and increment in bone mass in a population of women at particular risk of osteoporosis because of low bone mass. There were no differences between 2.5 mg ibandronate per day and placebo in terms of side effects, including complaints from the gastrointestinal tract, and ibandronate appeared safe for longer-term use in this dosing. Bone loss resumed at a normal postmenopausal rate when treatment was withdrawn. The response in bone mass and biochemical markers indicated that 2.5

mg ibandronate per day is equivalent to 10 mg alendronate per day in postmenopausal women. Our studies of two recently developed biochemical markers, urine CTX and serum total OC, showed that bone turnover was lowest in the premenopausal period, where these biochemical markers furthermore revealed a negative association with bone mass. It indicated that increased bone turnover contributes to a small premenopausal bone loss and resulting lowered bone mass. In consistence, a small premenopausal bone loss was observed in some regions of the hip. The biochemical markers increased at the time of menopause, consistent with initiation of the postmenopausal bone loss, and became gradually more negatively associated with bone mass as time past the menopause increased. The biochemical markers were furthermore higher in postmenopausal women with low bone mass, consistent with the characterization of postmenopausal osteoporosis as a condition with increased bone turnover. Our results consistently indicated a central role of increased bone turnover for development of low bone mass and osteoporosis. It is, however, also important to stress that the associations between biochemical markers and bone mass were too weak to allow for a valid individual estimation of bone mass based on biochemical markers. In contrast, the biochemical markers were shown as valid tools for monitoring and prediction of treatment effect of bisphosphonates. CTX, NTX, and total OC revealed the best performance characteristics in this respect. Six months after start of treatment, the level of suppression of these biochemical markers of bone resorption and formation accurately reflected the size of the 1-2 year response in bone mass in groups of women treated with bisphosphonate. This was a clear advance over bone densitometry, which has a precision error in the area of the anticipated yearly bone mass response during bisphosphonate therapy. The relationship was consistent during treatment with alendronate or ibandronate and in younger or elderly postmenopausal women. In individual patients, cut-off values of an about 40% decrease in urine CTX or NTX and an about 20% decrease in total OC validly predicted long-term prevention of bone loss. The sensitivity of prediction was high, but the specificity low. This implicated that the biochemical markers could be used as an exact method to detect "responders" to therapy, whereas "non-responders" to bisphosphonate treatment should be detected with bone densitometry in patients who do not reveal a decrease below the cut-off value in the biochemical marker during treatment. However, before such approach can be generally recommended the cut-off values of the biochemical markers should be validated in future clinical trials of bisphosphonate. Postmenopausal osteoporosis develops slowly over many years and mainly becomes a significant individual and socio-economic health problem 1-3 decades after the menopause. Prevention of postmenopausal osteoporosis by bisphosphonates is therefore likely to imply a treatment regimen of at least a decade, as presently recommended for HRT (Consensus Development Statement 1997). However, future cost-effectiveness studies should reveal when bisphosphonate treatment should ideally be initiated. Our studies showed that the bisphosphonates were effective over the range from general recommendation (recently postmenopausal women with normal bone mass) to a reservation for women at particular risk of osteoporosis (elderly women, thin women, or women with osteopenia). Presently available biochemical markers could be used for groupwise and individual monitoring and prediction of treatment response. Most presently available biochemical markers, however, have the drawback of a low specificity. Recent studies of CTX measured in serum are promising, and indicate that this new biochemical marker might have overcome these drawbacks due to a pronounced response to treatment and a low long-term biological variation (Christgau et al. 1998b, Rosen et al. 1998, and 2000)

Intravenous bisphosphonate prevents symptomatic osteoporotic vertebral collapse in patients after liver transplantation.

Reeves HL, Francis RM, Manas DM, et al.

*Liver Transpl Surg.* 1998 Sep; 4(5):404-9.

Osteoporosis is common in patients with chronic cholestatic liver disease, and atraumatic spinal fracture is a recognized complication after orthotopic liver transplantation. Bisphosphonates are potent inhibitors of osteoclast bone resorption and have been successfully used to treat postmenopausal osteoporosis. We examined whether preoperative bone mineral density can predict the risk of fracture after orthotopic liver transplantation and whether intravenous bisphosphonate can prevent fractures in high-risk patients. Beginning in February 1993, standard bone mineral density measurements of the lumbar spine were performed as part of routine pretransplantation assessment. On the basis of a preliminary analysis from January 1995, patients with a lumbar spine bone mineral density of <0.84 g/cm2, or <84% of the predicted value (age/sex), were treated with intravenous bisphosphonate (pamidronate disodium) every 3 months before and for 9 months after liver transplantation. Bone mineral density measurements were available in 90 of 136 consecutive first transplants performed in our unit from February 1993 to September 1996. Before the use of pamidronate, 7 patients sustained symptomatic vertebral fractures. Their mean spine bone mineral density was lower than in the 38 patients with no clinical evidence of fracture (81.8% +/- 12.3% v 94.2% +/- 10.2%; P = ".006)." Since the introduction of pamidronate, no symptomatic vertebral fractures have occurred. Of 29 surviving patients with bone mineral density <0.84 g/cm2 before transplantation, 38% who did not receive treatment with pamidronate suffered spontaneous fracture, whereas 0 of 13 who received treatment suffered such a complication. A low lumbar spine bone mineral density is associated with a high risk of symptomatic vertebral fracture after liver transplantation. These results suggest that this risk is considerably reduced by the administration of intravenous bisphosphonate before and after transplantation

Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis.

Reid IR, Wattie DJ, Evans MC, et al.

*J Clin Endocrinol Metab.* 1994 Dec; 79(6):1595-9.

There is a need for effective and acceptable therapies for postmenopausal osteoporosis. The bisphosphonates show promise in this role, but the effects of the potent bisphosphonates in established osteoporosis have not yet been reported. We performed a 2-yr, randomized, double blind, placebo-controlled trial of pamidronate (150 mg/day) in 48 postmenopausal osteoporotic women. Bone mineral density of the total body, lumbar spine, and proximal femur was measured every 6 months by dual energy x-ray absorptiometry. Bone mineral density increased progressively in the total body (1.9 +/- 0.7%; P < 0.01), lumbar spine (7.0 +/- 1.0%; P < 0.0001), and femoral trochanter (5.4 +/- 1.3%; P < 0.001) in subjects receiving pamidronate, but did not change significantly in those receiving placebo. There were significant decreases in bone density at both the femoral neck (P < 0.02) and Ward's triangle (P < 0.01) in subjects taking placebo, which did not occur in the pamidronate group. The differences between the treatment groups were significant at all sites (0.0001 < P < 0.05) except Ward's triangle. Vertebral fracture rates were 13/100 patient yr in the pamidronate group and 24/100 patient yr in those receiving placebo (P = "0.07)," and there was a nonsignificant trend toward height loss being less in those receiving pamidronate (P = "0.16)." It is concluded that pamidronate is an effective therapy in postmenopausal osteoporosis

Intravenous zoledronic acid in postmenopausal women with low bone mineral density.

Reid IR, Brown JP, Burckhardt P, et al.

*N Engl J Med.* 2002 Feb 28; 346(9):653-61.

BACKGROUND: Bisphosphonates are effective agents for the management of osteoporosis. Their low bioavailability and low potency necessitate frequent administration on an empty stomach, which may reduce compliance. Gastrointestinal intolerance limits maximal dosing. Although intermittent intravenous treatments have been used, the optimal doses and dosing interval have not been systematically explored. METHODS: We studied the effects of five regimens of zoledronic acid, the most potent bisphosphonate, on bone turnover and density in 351 postmenopausal women with low bone mineral density in a one-year, randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25 mg, 0.5 mg, or 1 mg at three-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, six months apart. Lumbar-spine bone mineral density was the primary end point. RESULTS: There were similar increases in bone mineral density in all the zoledronic acid groups to values for the spine that were 4.3 to 5.1 percent higher than those in the placebo group (P<0.001) and values for the femoral neck that were 3.1 to 3.5 percent higher than those in the placebo group (P<0.001). Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Myalgia and pyrexia occurred more commonly in the zoledronic acid groups, but treatment-related dropout rates were similar to that in the placebo group. CONCLUSIONS: Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis

The worldwide problem of osteoporosis: insights afforded by epidemiology.

Riggs BL, Melton LJ, III.

*Bone.* 1995 Nov; 17(5 Suppl):505S-11S.

Osteoporosis is one of the major problems facing women and older people of both sexes. The morbid event in osteoporosis is fracture. However, the definition of osteoporosis should not require the presence of fractures but only a decrease in bone mass that is associated with an unacceptably high risk of fracture. In the USA, approximately 1.5 million fractures annually are attributable to osteoporosis: these include 700,000 vertebral fractures, 250,000 distal forearm (Colles') fractures, 250,000 hip fractures, and 300,000 fractures of other limb sites. The lifetime risk of fractures of the spine (symptomatic), hip, and distal radius is 40% for white women and 13% for white men from 50 years of age onwards. Following a hip fracture, there is a 10%-20% mortality over the subsequent 6 months, 50% of sufferers will be unable to walk without assistance, and 25% will require long-term domiciliary care. Contrary to prevailing opinion, the morbidity and suffering associated with wrist and spine fractures are also considerable. The annual cost of osteoporosis to the US healthcare system is at least $5-$10 billion with similar incidence and cost in other developed countries. These already high costs will increase further with continued aging of the population. In addition, the population explosion in underdeveloped countries will change the demography of osteoporosis; for example, the incidence of hip fracture, and, presumably, other osteoporotic fractures will increase four-fold worldwide during the next 50 years and the attendant costs will threaten the viability of the healthcare systems of many countries. Unless decisive steps for preventive intervention are taken now, a catastrophic global epidemic of osteoporosis seems inevitable

Bisphosphonates: from the laboratory to the clinic and back again.

Russell RG, Rogers MJ.

*Bone.* 1999 Jul; 25(1):97-106.

Bisphosphonates (BPs) used as inhibitors of bone resorption all contain two phosphonate groups attached to a single carbon atom, forming a "P-C-P" structure. The bisphosphonates are therefore stable analogues of naturally occuring pyrophosphate-containing compounds, which now helps to explain their intracellular as well as their extracellular modes of action. Bisphosphonates adsorb to bone mineral and inhibit bone resorption. The mode of action of bisphosphonates was originally ascribed to physico-chemical effects on hydroxyapatite crystals, but it has gradually become clear that cellular effects must also be involved. The marked structure-activity relationships observed among more complex compounds indicate that the pharmacophore required for maximal activity not only depends upon the bisphosphonate moiety but also on key features, e.g., nitrogen substitution in alkyl or heterocyclic side chains. Several bisphosphonates (e.g., etidronate, clodronate, pamidronate, alendronate, tiludronate, risedronate, and ibandronate) are established as effective treatments in clinical disorders such as Paget's disease of bone, myeloma, and bone metastases. Bisphosphonates are also now well established as successful antiresorptive agents for the prevention and treatment of osteoporosis. In particular, etidronate and alendronate are approved as therapies in many countries, and both can increase bone mass and produce a reduction in fracture rates to approximately half of control rates at the spine, hip, and other sites in postmenopausal women. In addition to inhibition of osteoclasts, the ability of bisphosphonates to reduce the activation frequency and birth rates of new bone remodeling units, and possibly to enhance osteon mineralisation, may also contribute to the reduction in fractures. The clinical pharmacology of bisphosphonates is characterized by low intestinal absorption, but highly selective localization and retention in bone. Significant side effects are minimal. Current issues with bisphosphonates include the introduction of new compounds, the choice of therapeutic regimen (e.g., the use of intermittent dosing rather than continuous), intravenous vs. oral therapy, the optimal duration of therapy, the combination with other drugs, and extension of their use to other conditions, including steroid-associated osteoporosis, male osteoporosis, arthritis, and osteopenic disorders in childhood. Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of osteoclasts. It is likely that bisphosphonates are internalized by osteoclasts and interfere with specific biochemical processes and induce apoptosis. The molecular mechanisms by which these effects are brought about are becoming clearer. Recent studies show that bisphosphonates can be classified into at least two groups with different modes of action. Bisphosphonates that closely resemble pyrophosphate (such as clodronate and etidronate) can be metabolically incorporated into nonhydrolysable analogues of ATP that may inhibit ATP-dependent intracellular enzymes. The more potent, nitrogen-containing bisphosphonates (such as pamidronate, alendronate, risedronate, and ibandronate) are not metabolized in this way but can inhibit enzymes of the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the posttranslational modification of small GTPases. The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explains the loss of osteoclast activity and induction of apoptosis. These different modes of action might account for subtle differences between compounds in terms of their clinical effects. In conclusion, bisphosphonates are now established as an important class of drugs for the treatment of bone diseases, and their mode of action is being unravelled. As a result, their full therapeutic potential is gradual

Steroid-induced osteoporosis.

Sambrook PN.

*Ann Acad Med Singapore.* 2002 Jan; 31(1):48-53.

INTRODUCTION: Corticosteroids have major effects on calcium metabolism, leading to accelerated osteoporosis and fracture. METHODS: This review will attempt to summarise current knowledge about their effects in light of new information and important remaining questions, especially with respect to management of this common condition. RESULTS: Corticosteroids affect bone through multiple pathways, influencing both bone formation and bone resorption. Evidence from randomised trials suggests that postmenopausal women receiving corticosteroids are at greatest risk of rapid bone loss and consequent fracture and should be actively considered for prophylaxis. Based upon available evidence, the rank order of choice for prophylaxis would be a bisphosphonate followed by a vitamin D metabolite or hormone replacement. CONCLUSIONS: With early therapy, corticosteroid bone loss can be effectively prevented or reversed

Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk.

Schairer C, Lubin J, Troisi R, et al.

*JAMA.* 2000 Jan 26; 283(4):485-91.

CONTEXT: Whether menopausal hormone replacement therapy using a combined estrogen-progestin regimen increases risk of breast cancer beyond that associated with estrogen alone is unknown. OBJECTIVE: To determine whether increases in risk associated with the estrogen-progestin regimen are greater than those associated with estrogen alone. DESIGN: Cohort study of follow-up data for 1980-1995 from the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. SETTING: Twenty-nine screening centers throughout the United States. PARTICIPANTS: A total of 46355 postmenopausal women (mean age at start of follow-up, 58 years). MAIN OUTCOME MEASURE: Incident breast cancers by

recency, duration, and type of hormone use. RESULTS: During follow-up, 2082 cases of breast cancer were identified. Increases in risk with estrogen only and estrogen-progestin only were restricted to use within the previous 4 years (relative risk [RR], 1.2 [95% confidence interval [CI], 1.0-1.4] and 1.4 [95% CI, 1.1-1.8], respectively); the relative risk increased by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users, after adjustment for mammographic screening, age at menopause, body mass index (BMI), education, and age. The P value associated with the test of homogeneity of these estimates was .02. Among women with a BMI of 24.4 kg/m2 or less, increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. These associations were evident for the majority of invasive tumors with ductal histology and regardless of extent of invasive disease. Risk in heavier women did not increase with use of estrogen only or estrogen-progestin only. CONCLUSION: Our data suggest that the estrogen-progestin regimen increases breast cancer risk beyond that associated with estrogen alone

Exposure of infants to phyto-oestrogens from soy-based infant formula.

Setchell KD, Zimmer-Nechemias L, Cai J, et al.

*Lancet.* 1997 Jul 5; 350(9070):23-7.

BACKGROUND: The isoflavones genistein, daidzein, and their glycosides, found in high concentrations in soybeans and soy-protein foods, may have beneficial effects in the prevention or treatment of many hormone-dependent diseases. Because these bioactive phyto-oestrogens possess a wide range of hormonal and non-hormonal activities, it has been suggested that adverse effects may occur in infants fed soy-based formulas. METHODS: To evaluate the extent of infant exposure to phyto-oestrogens from soy formula, the isoflavone composition of 25 randomly selected samples from five major brands of commercially available soy-based infant formulas were analysed, and the plasma concentrations of genistein and daidzein, and the intestinally derived metabolite, equol, were compared in 4-month-old infants fed exclusively soy-based infant formula (n = 7), cow-milk formula (n = 7), or human breast-milk (n = 7). FINDINGS: All of the soy formulas contained mainly glycosides of genistein and daidzein, and the total isoflavone content was similar among the five formulas analysed and was related to the proportion of soy isolate used in their manufacture. From the concentrations of isoflavones in these formulas (means 32-47 micrograms/mL), the typical daily volume of milk consumed, and average bodyweight, a 4-month-old infant fed soy formula would be exposed to 28-47 per day, or about 4.5-8.0 mg/kg bodyweight per day, of total isoflavones. Mean (SD) plasma concentrations of genistein and daidzein in the seven infants fed soy-based formulas were 684 (443) ng/mL and 295 (60) ng/mL, respectively, which was significantly greater ($p < 0.05$) than in the infants fed either cow-milk formulas (3.2 [0.7] and 2.1 [0.3] ng/mL), or human breast-milk (2.8 [0.7] and 1.4 [0.1] ng/mL), and an order of magnitude higher per bodyweight than typical plasma concentrations of adults consuming soy foods. INTERPRETATION: The daily exposure of infants to isoflavones in soy infant-formulas is 6-11 fold higher on a bodyweight basis than the dose that has hormonal effects in adults consuming soy foods. Circulating concentrations of isoflavones in the seven infants fed soy-based formula were 13000-22000 times higher than plasma oestradiol concentrations in early life, and may be sufficient to exert biological effects, whereas the contribution of isoflavones from breast-milk and cow-milk is negligible

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

Shiraki M, Shiraki Y, Aoki C, et al.

*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

Effects of fluoride on rat vertebral body biomechanical competence and bone mass.

Sogaard CH, Mosekilde L, Schwartz W, et al.

*Bone.* 1995 Jan; 16(1):163-9.

For more than 30 years, sodium fluoride has been a commonly used therapeutic agent for established osteoporosis because of its repeatedly documented anabolic effect on trabecular bone mass. Recent clinical and experimental studies have, however, indicated a possible detrimental effect of fluoride on bone strength. Thus, the efficacy of fluoride therapy remains a controversial issue. The aim of this study was to investigate the effect of fluoride on both vertebral bone mass and quality in rats. Twenty-nine 3-month-old, female rats were randomized into three groups. One group served as a control group, and the other two groups received fluoridated water at different doses (100 ppm and 150 ppm). The rats were followed for 90 days. Three lumbar vertebrae were obtained from each rat, and changes in bone fluoride content, bone mass and biomechanical competence were assessed. The results revealed a significant increase in bone fluoride content, ash density and trabecular bone volume after fluoride treatment. Directly obtained load values and load corrected for cross-sectional area were constant. Load corrected for ash content, which is a measure of bone quality, decreased significantly after fluoride therapy. It is concluded that the increase in bone mass during fluoride treatment does not translate into an improved bone strength and that the bone quality declines. This investigation thereby supports the hypothesis of a possible negative effect of fluoride on bone quality

Two years' effectiveness of intravenous pamidronate (APD) versus oral fluoride for osteoporosis occurring in the postmenopause.

Thiebaud D, Burckhardt P, Melchior J, et al.

*Osteoporos Int.* 1994 Mar; 4(2):76-83.

Bisphosphonates seem to be effective as antiresorptive agents in the prevention and treatment of osteoporosis. However, the optimal dose and route of administration as well as the specific effects on cortical or trabecular bone have not been clarified. To compare pamidronate (APD) with fluoride (F) in the therapy of postmenopausal osteoporosis, 32 osteoporotic women were treated for 2 years either with APD (30 mg as a single intravenous infusion over 1 h every 3 months, n = 16, mean age 65 years) or with fluoride orally (20-30 mg F/day, n = 16, mean age 67 years) in an open study. Both groups received 1 g calcium and 1000 U vitamin D per day, but no estrogens or other drugs acting on bone. Both groups showed the same initial mean number of fractures per patient (2.8 and 2.7). Bone densitometry was performed every 6 months at three sites: lumbar spine and hip with dual-energy X-ray absorptiometry (BMD), distal forearm with single photon absorptiometry and lumbar spine with quantitative computed tomography. Biochemical assessment was performed in blood and urine every 3 months. Lumbar BMD (g/cm2, mean +/- SEM) increased from 0.632 (+/- 0.030) at time 0 to 0.696 (+/- 0.028) at 24 months in the APD group ($p < 0.001$), and from 0.684 (+/- 0.025) to 0.769 (+/- 0.028) in the fluoride group ($p < 0.001$). Femoral neck BMD increased significantly from 0.558 (+/- 0.025) to 0.585 (+/- 0.025) ($p < 0.01$) in the APD group, whereas it did not change in the fluoride group.(ABSTRACT TRUNCATED AT 250 WORDS)

The effects of fluoridated water on bone strength.

Turner CH, Akhter MP, Heaney RP.

*J Orthop Res.* 1992 Jul; 10(4):581-7.

Fluoride from fluoridated water accumulates not only in the enamel of teeth but also in the skeleton. The effects of fluoridated water on the skeleton are not well understood, yet there is some evidence that fluoridated water consumption increases the incidence of fractures. In the present study, femoral bending strength was measured in rats on fluoride intakes that ranged from low levels to levels well above natural high fluoride drinking water. Bone strength followed a biphasic relationship with bone fluoride content. Fluoride had a positive effect on bone strength for lower fluoride intakes and a negative influence on bone strength for higher fluoride intakes. The vertebral fluoride content at which femoral strength was maximum was between 1,100 and 1,500 ppm. The increase in femoral strength at this fluoride level was not accompanied by an increase in femoral bone density. The optimal fluoride content is within the range of bone fluoride contents found in persons living in regions with fluoridated water (1 ppm) for greater than 10 years

Fluoride treatment increased serum IGF-1, bone turnover, and bone mass, but not bone strength, in rabbits.

Turner CH, Garetto LP, Dunipace AJ, et al.

*Calcif Tissue Int.* 1997 Jul; 61(1):77-83.

We hypothesized that fluoride partly acts by changing the levels of circulating calcium-regulating hormones and skeletal growth factors. The effects of oral fluoride on 24 female, Dutch-Belted, young adult rabbits were studied. The rabbits were divided into two study groups, one control and the other receiving about 16 mg fluoride/rabbit/day in their drinking water. After 6 months of fluoride dosing, all rabbits were euthanized and bone and blood samples were taken for analyses. Fluoride treatment increased serum and bone fluoride levels by over an order of magnitude (P 0.4). BAP was increased 37% (P < 0.05) by fluoride; serum TRAP was increased 42% (P < 0.05); serum IGF-1 was increased 40% (P < 0.05). Fluoride increased the vertebral BV/TV by 35% (P < 0.05) and tibial ash weight by 10% (P < 0.05). However, the increases in bone mass and bone formation were not reflected in improved bone strength. Fluoride decreased bone strength by about 19% in the L5 vertebra (P < 0.01) and 25% in the femoral neck (P < 0. 05). X-ray diffraction showed altered mineral crystal thickness in fluoride-treated bones (P < 0.001), and there was a negative association between crystal width and fracture stress of the femur (P < 0.02). In conclusion, fluoride's effects on bone mass and bone turnover were not mediated by PTH. IGF-1 was increased by fluoride and was associated with increased bone turnover, but was not correlated with bone formation markers. High-dose fluoride treatment did not improve, but decreased, bone strength in rabbits, even in the absence of impaired mineralization

Biomechanics of bone: determinants of skeletal fragility and bone quality.

Turner CH.

*Osteoporos Int.* 2002; 13(2):97-104.

Bone fragility can be defined by biomechanical parameters, including ultimate force (a measure of strength), ultimate displacement (reciprocal of brittleness) and work to failure (energy absorption). Bone fragility is influenced by bone size, shape, architecture and tissue 'quality'. Many osteoporosis treatments build bone mass but also change tissue quality. Antiresorptive therapies, such as bisphosphonates, substantially reduce bone turnover, impairing microdamage repair and causing increased bone mineralization, which can increase the brittleness of bone. Anabolic therapies, such as parathyroid hormone (PTH-(1-84)) or teriparatide (PTH-( 1-34)), increase bone turnover and porosity, which offset some of the positive effects on bone strength. Osteoporosis therapies may also affect bone architecture by causing the redistribution of bone structure. Restructuring of bone during treatment may change bone fragility, even in the absence of drug effects on bone mineral density (BMD). This effect may explain why some drugs can affect fracture incidence disproportionately to changes in BMD. For instance, in a recent clinical trial, PTH-(1-34) therapy caused a dose-related increase in spinal BMD without any dose-dependent effect on the observed decrease in spinal fracture incidence. This apparent disassociation between spinal BMD and bone fragility is probably due to effects of PTH-(1-34) on bone architecture within vertebral bodies. While it has been shown that BMD is highly heritable, bone mineral distribution and architecture are also under strong genetic influence. Recent findings suggest that different genes regulate trabecular and cortical structures within lumbar vertebrae, producing a wide range of bone architectural designs. These findings suggest that there is no single optimal bone architecture; instead many different architectural solutions produce adequate bone strength

Vitamin K and bone health.

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*Nutrition.* 2001 Oct; 17(10):880-7.

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 can not 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

[Bisphosphonate therapy in osteoporosis. Inhibition of trabecular perforation by aminobisphosphonate].

Wuster C, Heilmann P.

*Fortschr Med.* 1997 Oct 20; 115(29):37-42.

After many years of experience with bisophosphonates in the treatment of "tumor osteopathy" and Paget's disease, these substances have now also been approved for use in the treatment of osteoporosis. Owing to their high affinity for calcium hydroxyapatite, the bisphosphonates are deposited in the bony surface, and the aminobisphosphonates exert their effect at the site of active resorption via direct inhibition of active osteoclasts. As a result of this inhibition of the osteoclastic bone resorption, trabecular perforation is reduced and during the course of bone remodelling by the activity of the osteoblasts, boneformation occurs. In addition to an increase in bone density, both etidronate and alendronate have been shown to inhibit vertebral fractures in patients with osteoporosis. In addition, in patients with preexisting fractures, alendronate is able, at the same time, to lower the incidence of fractures of the femoral neck. With proper administration, the associated occasional gastrointestinal side effects can be avoided. The introduction of bisphosphonates into the treatment of osteoporosis is definitely an enrichment of the therapeutic spectrum in conjunction with the basic treatment comprising calcium, vitamin D, diet and physical measures

Teenaged girls, carbonated beverage consumption, and bone fractures.

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*Arch Pediatr Adolesc Med.* 2000 Jun; 154(6):610-3.

OBJECTIVE: To determine the possible association between carbonated beverage consumption and bone fractures among teenaged girls given the awareness of the concern about the impact of carbonated beverage consumption on children's health. SETTING: An urban high school. METHODS: A cross-sectional (retrospective) study. Four hundred sixty 9th- and 10th-grade girls attending the high school participated in this study by completing a self-administered questionnaire relating to their physical activities and personal and behavioral practices. The school system and the Harvard School of Public Health Institutional Review Boards approved the study. The girls' self-reports on physical activity, carbonated beverage consumption, and bone fractures are analyzed. RESULTS: In the total sample, carbonated beverage consumption and bone fractures are associated: odds ratio = 3.14 (95% confidence limit, 1.45, 6.78), P = .004. Among physically active girls, the cola beverages, in particular, are highly associated with bone fractures: odds ratio = 4.94 (95% confidence limit, 1.79, 13.62), P = .002. CONCLUSIONS: The results reported confirm previous findings, but the mechanism by which cola drinks are associated with bone fractures in physically active girls has neither been fully explored nor determined. Nevertheless, national concern and alarm about the health impact of carbonated beverage consumption on teenaged girls is supported by the findings of this study. The results have policy implications for improving the dietary practices and health of children

[Estrogen therapy in women with postmenopausal osteoporosis].

Zarcone R, Carfora E, Sergio F, et al.

*Minerva Ginecol.* 1997 Jul; 49(7-8):355-9.

BACKGROUND: The effects of estrogen-therapy on bone mineral density and the incidence of fractures in 132 women with postmenopausal osteoporosis have been studied. MATERIALS AND METHODS: The patients were randomly assigned to receive placebo or estrogens (0.15 or 0.3 or 0.625 mg) for 64 months. Bone mineral density of the lumbar spine was measured by dual-energy X-ray absorptiometry with the use of Hologic QR-1000 densitometers, in all women. RESULTS: A significant increase in bone mineral density was observed in women receiving estrogens, whereas in those receiving placebo there was a decrease in bone mineral density