

Bone marrow transplantation leads to femoral bone loss

Allogeneic bone marrow transplantation is associated with a preferential femoral neck bone loss

Buchs N, Helg C, Collao C, Chapuis B, Slosman D, Bonjour J-P, Rizzoli R, *Osteoporos Int* 2001;12:880-886.

Background: Bone marrow transplantation has saved the lives of many patients with malignant and non-malignant blood disorders. Osteoporosis, however, an important complication of organ transplantation, can dramatically lessen a patient's quality of life. Studies of kidney, heart, liver, and lung transplantation have reported a high risk for fractures associated with both the underlying disease and the potent immunosuppressive and chemotherapy required for successful transplantation.

Study and Results: BMD was evaluated in bone marrow transplant (BMT) patients (n = 102) at the time of transplantation and during a 13-year follow-up period. Lumbar spine BMD was normal and did not differ for subjects studied during the first few months after transplantation (group A) and those studied 60 months later (group B). Femoral neck Z and T-scores were significantly lower in patients from group B compared with those from group A (T-scores -0.84 vs. -0.22). Osteopenia was present in 35% of group A patients and 43% of group B patients. Osteoporosis was found in 7% of group B patients, but in none of the group A patients. A longitudinal study of a subgroup of patients measured at transplantation and 6 and 12 months later found that only femur neck BMD was reduced significantly compared with baseline. Bone loss after BMT was less than that experienced by patients with solid organ transplants, probably because of the younger age (premenopausal for women) of the recipients, and the shorter duration of disease and treatment prior to transplantation.

Conclusion: Bone loss after bone marrow transplantation was higher for femoral neck BMD than for spine or total body BMD. Most bone loss occurred during the first 6 months after transplantation.

Calcium and exercise beneficial for bone in children and adolescents

The influence of calcium intake and physical activity on bone mineral content and bone size in healthy children and adolescents

Molgaard C, Thomsen BL, Michaelsen KF, *Osteoporos Int* 2001;12:887-894.

Background: Optimizing peak bone mass in childhood and adolescence might have a significant effect on risk of osteoporosis later in life. Genetics plays the major role in determining peak bone mass, but lifestyle factors also contribute significantly.

Study and Results: Healthy girls (n = 192) and boys (n = 140) aged 5 to 19 years were studied at baseline and after one year to determine the effect of calcium intake and physical activity on bone size, increase in bone area, and total body bone mineral content. Calcium intake and physical activity were not associated with bone area adjusted for height and weight. Increases in bone area showed a slightly positive association with calcium intake in boys, but not girls. BMC showed a significant positive association with calcium intake in girls (p = 0.03) and a borderline positive association in boys (p = 0.07). BMC showed a borderline positive association with physical activity in boys (p = 0.07) but not in girls (p = 0.7).

Conclusion: BMC adjusted for body size was positively associated with average calcium intake in school-aged children.

DXA records significant BMD loss in patients with stem cell transplantation

Loss of bone mass and vitamin D deficiency after hematopoietic stem cell transplantation: standard prophylactic measures fail to prevent osteoporosis

Massenkeil G, Fiene C, Rosen O, Michael R, Reisinger W, Arnold R, *Leukemia* 2001;15:1701-1705.

Background: Successful treatment and long-term survival of many patients with blood cell malignancies (e.g., leukemia) have increased interest in effects of treatment on bone metabolism. The substantial bone loss that occurs in patients with acute leukemias is not surprising given the close developmental relationship of osteoblasts and osteoclasts with blood stem cells. Stem cell transplantation (SCT) can cure leukemia and other malignant diseases of the blood, but chemotherapy, steroids, immobilization, and the body's graft-versus-host disease associated with transplantation and post-transplantation therapy has a decidedly negative effect on bone.

Study and Results: BMD and biochemical markers of bone metabolism were evaluated in 67 patients following SCT. Bone loss was common prior to SCT, and intensive chemotherapy, immobilization, and steroid therapy led to further bone loss after SCT. Osteopenia or osteoporosis was present in 49% of subjects prior to transplantation, and in 67% of patients six months after transplantation. Bone loss was evident in both cortical and trabecular bone. Biochemical markers confirmed a prolonged disturbance in bone metabolism following SCT. Vitamin D deficiency was observed in all patients 6 months after transplantation, possibly the result of nutritional restrictions, recommended UV protection, and gastrointestinal disturbances. Calcium and vitamin D supplementation were not sufficient to prevent bone loss.

Conclusion: Osteopenia and osteoporosis are common in patients prior to and after stem cell transplantation. Routine calcium and vitamin D supplementation during hospitalization was not sufficient to prevent bone loss associated with transplantation and post-transplantation treatment of malignant diseases of blood and blood forming tissues. Studies of other therapies to prevent bone loss in SCT survivors should be undertaken.

Low dose HRT effective in early postmenopausal women

Effects of low-dose continuous combined conjugated estrogens and medroxyprogesterone acetate on menopausal symptoms, body weight, bone density, and metabolism in postmenopausal women

Gambacciani M, Ciaponi M, Cappagli B, Genazzani AR, *Am J Obstet Gynecol* 185:1180-1185.

Background: Loss of estrogen production after menopause results in increased bone turnover and bone loss. Hormone replacement therapy (HRT) limits increased bone turnover and helps prevent postmenopausal osteoporosis. Compliance with HRT therapy over the long term has been poor, however, because of concerns about side effects associated with standard HRT regimens. Lower dose HRT may lessen unwanted side effects and increase compliance, while maintaining efficacy in terms of bone loss and fracture prevention. Lower dose HRT (LD-HRT) has been shown recently to relieve vasomotor symptoms and prevent bone loss in older postmenopausal women (>65 years of age). The effect of low dose HRT in relatively young postmenopausal women has not been studied adequately.

Study and Results: Sixty early postmenopausal women (aged 45 to 56 years) were randomized into two groups that received either continuous, combined LD-HRT (0.3 mg/day conjugated equine estrogens and 2.5 mg/day medroxyprogesterone acetate) plus 1000 mg calcium/day or 1000 mg calcium/day alone. Continuous LD-HRT effectively reduced menopausal symptoms (hot flushes and other clinical symptoms), eliminated bleeding in 87% of patients, and minimized side effects. Spine BMD (DPX) increased 1.6% after 12 months and 2.7% after 24 months in the LD-HRT group, but decreased 5.7% after 12 months and 7.9% after 24 months in the control group. Body mass index increased significantly with a 3% weight gain in the control group, but showed no significant change in the LD-HRT group.

Conclusions: LD-HRT was effective in reducing menopausal symptoms and provided protection against bone loss in early postmenopausal women.

Peripheral measurements of bone status were not important predictors of hip fractures 25 to 30 years later

Can metacarpal cortical area predict the occurrence of hip fracture in women and men over 3 decades of follow-up? Results from the Framingham Osteoporosis Study

Kiel DP, Hannan MT, Broe KE, Felson DT, Cupples LA, *J Bone Miner Res* 2001;16:2260-2266.

Background: The ability of a single measurement of bone status in middle-aged men and women to predict hip fracture far into the future has not been examined by any large prospective study. The Framingham Study was begun in 1948 to look for risk factors for heart disease in 5209 subjects from Framingham, Massachusetts. Surviving subjects have been reexamined every two years.

Study and Results: Radiogrammetry was used to measure cortical bone mass (bone area) of the second metacarpal from hand radiographs acquired from 1386 women and 1048 men at the 10th – 11th exam (1966-1970) as part of a Framingham Osteoporosis Study. The aim of the current study was to determine whether a single measurement of metacarpal cortical area could predict hip fracture 25 to 30 years later. There was no significant increase in overall hip fracture risk associated with metacarpal cortical area in women. This finding held true even when only women aged 65 years or older were followed for only 10 years. There was a suggestion of a significant association between metacarpal cortical area and intertrochanteric hip fracture (RR = 1.24) in women, but this association disappeared after correcting for confounders. Metacarpal cortical area was associated modestly (RR = 1.4) with risk of hip fracture in men.

Conclusion: Finger cortical area analyzed with radiogrammetry was only moderately predictive of hip fracture in men, and was not predictive of hip fracture in women 25 to 30 years later. Peripheral bone status did not appear to be an important predictor of hip fracture over a lengthy follow-up period.

Physical activity somewhat useful for lessening BMD loss in peri- and postmenopausal women

Leisure-time physical activity and rate of bone loss among peri- and postmenopausal women: a longitudinal study

Puntila E, Kroger H, Lakka T, Tuppurainen M, Jurvelin J, Honkanen R, *Bone* 2001;29:442-446.

Background: Physical activity has been shown to have some effect on BMD in training trials and some cross-sectional studies. Few studies have looked at the effect of regular, leisure-time, physical activity on BMD in a population-based study of middle-aged and elderly women.

Study and Results: BMD (DPX) and BMC of the lumbar spine and femoral neck were evaluated in 1873 peri- and postmenopausal women who completed a questionnaire that determined levels of leisure-time physical activity. Spine BMD and BMC loss over a 5.6-year follow-up period was less for women who participated in at least 1 hour/week of weight-bearing exercise than for sedentary women, especially among women whose only physical activity was walking or jogging. There was no effect of leisure-time, physical activity on femoral neck BMD and BMC.

Conclusion: Regular leisure-time, low impact exercise lessened BMD loss at the lumbar spine in peri- and early postmenopausal women, but was ineffective in limiting BMD loss at the femoral neck.

Risk factors known to affect BMD could guide densitometry decisions

Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature

Espallargues M, Sampietro-Colom L, Estrada MD, Sola M, del Rio L, Setoain J, Granados A, *Osteoporos Int* 2001;12:811-822.

Background: Fracture prediction with bone densitometry is most effective when evaluating subjects who are already at a heightened risk for osteoporotic fractures. Identification of risk factors for fracture that are associated with low BMD might improve overall fracture prediction.

Study and Results: A search of fracture risk studies from several large databases was carried out to identify and classify risk factors for fracture. Risk factors were classified into three groups based on the strength of their association with fracture. High risk factors (Relative Risk (RR) ≥ 2) included: a) low body mass index (<20-25 kg/m²) or low body weight (<40 kg), b) loss of weight, c) lack of exercise or physical activity, d) corticosteroid or anticonvulsant therapy, e) primary hyperparathyroidism, f) diabetes mellitus type I, g) anorexia nervosa, h) gastrectomy, i) pernicious anemia, and j) aging (>70 – 80 years of age). Relative risks of pertinent factors ranged from 2.9 to 3.8 for diabetes mellitus, 2.6 to 3.5 for hyperparathyroidism, 7.1 for anorexia, 1.6 to 3.8 for pernicious anemia, and 1.8 to 2.6 for gastrectomy. Prior osteoporotic fracture was also associated with a high risk of future fracture. Moderate risk factors (1

<RR<2) included a) female gender, b) active smoking, c) family history of osteoporotic fracture, d) surgical menopause, e) early menopause (<45 years), f) short fertile period (<30 years), g) late menarche (> 15 years), h) no lactation, i) low calcium intake (<500 to 850 mg/day), j) hyperparathyroidism, k) hyperthyroidism, l) diabetes mellitus (type II), and m) rheumatoid arthritis. Factors not contributing to fracture risk included caffeine, tea, nulliparity, fluoridated water, and thiazide diuretics.

Conclusion: Clinical risk factors used alone have little predictive value in identifying women with low BMD. Risk factors, however, could be used to identify women at high risk of fracture who would benefit most from bone densitometry.

Alendronate effective in treating primary osteoporosis in men

Alendronate treatment of established primary osteoporosis in men: results of a 2-year prospective study

Ringe JD, Faber H, Dorst A, *J Clin Endocrinol Metab*, 2001;86:5252-5255.

Background: Clinical trials of osteoporosis preventive therapies have been performed mainly on women. Osteoporotic fractures are substantially less common in men than women, but osteoporotic fractures in men account for nearly 30% of the total. Fractures occur less frequently in men than women because of larger bones, absence of a period equivalent to the menopause, and shorter life span in men. Clinical trials are necessary to document the efficacy of potential osteoporosis therapies in men.

Study and Results: The efficacy of alendronate (10 mg/day) and vitamin D (alfacalcidol, 1 μ /day) was evaluated over a two-year period in 134 men with primary osteoporosis. Spine and femur neck BMD (DPX) increased 2.8% and 2.2%, respectively, in men taking vitamin D, but increased 10.1% and 5.2% respectively, in men taking alendronate. Vertebral fractures occurred in 18.2% of men taking vitamin D and 7.4% of men taking alendronate, but this difference was not significant ($p = 0.07$). Alendronate and vitamin D therapies were both well tolerated. Results were very similar to those found previously in studies of postmenopausal women with osteoporosis.

Conclusion: Alendronate was effective in treating men with established primary osteoporosis.

BMD decreased in athletes with tibial stress syndrome

Abnormally decreased regional bone density in athletes with medial tibial stress syndrome

Magnusson HI, Westlin NE, Nyqvist F, Gardsell P, Seeman E, Karlsson MK, *Am J Sports Med* 2001;29:712-715.

Background: Localized tibial pain, referred to as medial tibial stress syndrome (MTSS), is encountered frequently in athletes, especially during periods of increased or altered type of physical activity. Scintigraphic studies that showed increased uptake of radioisotopes indicated increased skeletal metabolism in the affected region. Little information is known about the effect of MTSS on BMD in the affected and surrounding skeletal regions.

Study and Results: Young male athletes ($n = 18$) with MTSS participating in weight-bearing sports were compared with 16 control subjects and 18 athletes without MTSS who were experiencing the same level of exercise. Results showed that tibial BMD (DPX) of the painful region in subjects with MTSS was 15% lower than in control subjects and 23% lower than in athletes without MTSS. BMD at sites other than the tibia in MTSS subjects tended to be higher than BMD in controls, but lower than BMD levels of athletes without MTSS. Authors speculated that excessive BMD loss after onset of symptoms or less than optimal bone accrual during growth might have contributed to the substantial BMD deficit.

Conclusion: Tibial BMD was decreased in athletes with MTSS.

BMD reduced in premature children

Lower femoral neck bone mineral density in prepubertal former preterm girls

Zamora SA, Belli DC, Rizzoli R, Slosman DO, Bonjour J-P, *Bone* 2001;29:424-427.

Background: Events and stimuli that occur in the intrauterine environment and in the early postnatal period have been associated with profound effects on growth and development throughout lifetime. For example, cigarette smoking and excessive alcohol use during pregnancy have negative effects on skeletal growth and BMD in prepubertal children. The occasion of being born prematurely likewise might have significant skeletal effects.

Study and Results: BMC and BMD were evaluated in 25 healthy, white girls (age 7 to 9 years) who were born prematurely and compared with results from 50 age-matched controls. Repeat measurements were made after one year on 13 preterm and 13 control girls. Former preterm girls weighed less than term girls, but were similar for height. BMD adjusted for age, weight and height was lower than controls at the distal radius (0.28 vs. 0.30 g/cm²), femoral neck (0.59 vs. 0.64 g/cm²) and total hip (0.60 vs. 0.64 g/cm²), but was similar to controls at the radius shaft, femoral shaft, and lumbar spine. The deficit in femur neck BMD was about 0.5 SD. Authors noted that this BMD difference could be a clinically significant risk factor for postmenopausal fracture if persistent into adulthood. BMD remained low at the femur neck and total hip in the subgroup of preterm girls followed over 1 year.

Conclusion: Preterm girls were able to catch up to term girls in height, but were somewhat deficient in BMD at the femur and distal radius compared with controls. This BMD deficit might result in a higher risk for postmenopausal hip fracture. Further studies are necessary to determine whether preterm girls catch up to term girls after their adolescent growth spurt.

Heel Ultrasound (Achilles) associated with diminished cognitive function in octogenarians

Correlation between the bone mass, psychometric performances, and the levels of autonomy and autosufficiency in an elderly Italian population above 80 years of age

Maugeri D, Santangelo A, Abbate S, Barbagallo P, Lentini A, Motta M, Malaguarnera M, Speciale S, Testai M, Panebinco P, *Archiv Gerontol Geriatr* 2001;33:265-271.

Background: Recent studies have shown a strong relationship between BMD and cognitive abilities in the elderly. The interaction of age-related decline in physical activity with an increased incidence of various chronic and degenerative pathologies such as diabetes, hypertension, cardiac disorders, and obstructive chronic pulmonary disease may contribute to cognitive impairment and BMD deficits that greatly increase the risk of fracture in elderly subjects.

Study and Results: Bone status, cognitive and affective function, and measures of self-sufficiency were evaluated in 62 institutionalized octogenarians (Group A; mean age 84 years) and 63 non-institutionalized octogenarian controls (Group B; mean age 85 years). Bone status was evaluated with heel ultrasonometry (Achilles). Group A subjects had strongly decreased cognitive and affective function and serious impairments in self-sufficiency measurements compared with Group B subjects. T-scores, Z-scores, and Stiffness Index were -3.6, -1.2, and 59, respectively, for group A subjects and -1.2, 0.9, and 89, respectively, for Group B subjects. Z-scores were deficient in 71% of group A subjects compared with 46% of group B subjects.

Conclusion: Decreased BMD in Group A subjects was related predominantly to reduced physical activity prevalent among these institutionalized subjects. Reduced physical activity resulted, at least in part, from a decline in cognitive function associated with diminished mental and sensorial stimulation in the institutionalized environment.

Male bone strength benefits from greater periosteal bone deposition compared with women

Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss.

Duan Y, Turner CH, Kim B-T, Seeman E, *J Bone Miner Res* 2001;16:2267-2275.

Background: Incidence of vertebral fracture increases with age in both men and women, but the overall incidence is lower in men. This dissimilarity in incidence could result from a difference in the amount of bone deposited on the outer, periosteal bone surfaces compared with the amount resorbed concurrently

from the inner, endosteal margins of bone adjacent to the marrow space. The rate of bone resorption is similar in men and women, but men appear to have greater bone formation on the outer surfaces than women. This difference results in substantially less net bone loss and a greater vertebral cross-sectional area (CSA) in men. This preferential redistribution of bone in males results in the distribution of weight-bearing loads over a larger CSA, decreasing the likelihood of fracture

Study and Results: Healthy men (n = 327) and women (n = 686) ranging in age from 18 to 92 years, and 76 patients with spine fractures were evaluated with DXA (DPX) for PA spine and lateral spine BMD. Vertebral heights were derived from lateral scans. Men lost about 6% of vertebral BMC during aging, while women lost nearly 27%. Men appeared to resorb more bone than women (3.7g vs. 3.1g), but men deposited nearly three-fold more bone on periosteal surfaces than women over a lifetime. Greater bone deposition on periosteal surfaces increased CSA three-fold, and led to more than a two-fold decrease in load imposed per unit of CSA.

Conclusion: Both sexes lost bone with aging, but greater periosteal bone deposition in males increased the CSA and decreased the load imposed per unit CSA, resulting in a lower incidence of vertebral fracture in men than women.

Pregnancy and lactation not significant risk factors for osteoporosis

Pregnancy and lactation confer reversible bone loss in humans

Karlsson C, Obrant KJ, Karlsson M, *Osteoporos Int* 2001;12:828-834.

Background: Estrogen is important for achieving and maintaining healthy levels of BMD. Circulating estrogen increases during pregnancy and declines after birth. Low estrogen levels are maintained throughout the lactation period and are not restored to prepregnancy levels until ovulation resumes. Thus, women with multiple pregnancies experience extended periods of elevated and then depressed estrogen levels. Other factors such as activity level, nutrition, body weight, and other lifestyle factors also have an influence on BMD.

Study and Results: BMD (DPX) and body composition were studied in 73 healthy, premenopausal women (mean age 29 years) shortly after a normal pregnancy and delivery and 55 non-pregnant healthy women who had no pregnancies or breastfeeding during the prior year. The effect of lactation on BMD was assessed in three groups: a) non-breastfeeding mothers, b) mothers breastfeeding for 1 to 6 months, and c) mothers breastfeeding for more than 6 months. New mothers had 7.6% lower spine BMD and 4% lower total body BMD compared with controls, after adjusting for differences in fat and lean mass. Women who did not breastfeed showed small, but not significant decreases in BMD during the first 5 months after delivery. Spine BMD increased from the fifth to twelfth month post-delivery and was higher than baseline 12 months after delivery. Women who breastfed for 1 to 6 months showed increased BMD (3.9%) at the spine, but a significant BMD loss (~3.1%) at the femoral neck 5 months and 12 months after delivery. Mothers who breastfed for 6 to 12 months showed a small BMD deficit at the lumbar spine and Ward's triangle regions during the first 5 months, and no additional loss over the following 7 months.

Conclusion: Pregnancy and breastfeeding resulted in a BMD loss at some skeletal sites that was not restored completely 12 months after delivery. BMD of women with 4 or more pregnancies, however, did not differ from BMD of women with 2 or fewer pregnancies, and the duration of lactation was not related to BMD. Authors concluded that multiple pregnancies or extended periods of lactation were not significant risk factors for future osteoporosis.

Spine BMD affected negatively by short-term treatment of asthma with oral corticosteroids, but not by long-term treatment with inhaled corticosteroids

Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients

Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M, *Chest* 2001;120:1468-1473.

Background: Inhaled corticosteroids (ICSs) are used commonly over lengthy periods as the main therapy for controlling asthma, a generally incurable disease. There have been conflicting reports about the effect of ICSs on bone metabolism and BMD.

Study and Results: Spine BMD was evaluated at baseline and at a mean of 4.2 years later in 15 men and 20 postmenopausal women (mean age 60.6 years at second evaluation) who had been treated with beclomethasone dipropionate (BDP) and short courses of oral corticosteroids (SC-OCS). The average frequency of SC-OCS was 1.9 ± 2.7 per year. Spine BMD did not decrease significantly during the study period in patients receiving either low or high doses of BDP, but patients who had frequent short courses of oral corticosteroids (i.e., >2.5 times/year) showed significantly greater bone loss than patients receiving less frequent SC-OCS.

Conclusion: Inhaled corticosteroid therapy did not affect spine BMD, but frequent use of short courses of oral corticosteroids appeared to have a negative effect on spine BMD.

BMD at peripheral sites strong predictor of subsequent fractures in large USA population study

Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women – Results from the National Osteoporosis Risk Assessment

Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, Berger ML, Santora AC, Sherwood LM, *JAMA* 2001;286:2815-2822.

Background: BMD is the best single predictor of fracture risk in asymptomatic postmenopausal women, and central densitometry with DXA is regarded as the best method to measure spine and femur BMD. Densitometry equipment that measures peripheral sites such as the forearm, however, is portable, less expensive, and potentially available to a larger portion of the population. The National Osteoporosis Risk Assessment (NORA) was launched as an observational study of osteoporosis among postmenopausal women in primary care practices.

Study and Results: BMD was assessed longitudinally in over 200,000 postmenopausal women selected randomly from eligible women in 34 states. Eligibility criteria included ability to walk and visit physician offices, and no current use of bisphosphonates, calcitonin, or raloxifene. Estrogen use was acceptable. Lifestyle behaviors, medication use, and family history of fractures were determined by questionnaire. Peripheral measurements were made with heel DXA (n=67,566), finger DXA (15,011), single x-ray absorptiometry (SXA) (n=107,897) of the heel, or heel ultrasonography (n=9686). Osteopenia and osteoporosis were defined according to WHO guidelines. Osteopenia or osteoporosis was found at one or more peripheral sites in 39.6% and 7.2% of women, respectively.

Percent of women with osteopenia or osteoporosis at peripheral measurement sites

%	SXA-Heel	DXA-Forearm	DXA-Finger	QUS-heel
Osteopenia (T-score -1 to -2.5)	44%	35%	28%	34%
Osteoporosis (T-score <-2.5)	5%	10%	14%	3%

Advancing age was the most important risk factor for low BMD. Other risk factors included, poor self-rated health, personal fracture history, maternal history of osteoporosis, and maternal history of fracture after age 45 years. The risk of osteoporosis was about 50% greater for Asian women and 30% greater for Hispanic women compared with white women. The risk of fracture, however, was no different for Hispanic women and lower for Asians compared with white women. The risk of fracture for Native Americans was similar to the risk for white women. Osteoporosis was increased among current and past smokers and among current users of cortisone. Decreased risk for osteoporosis was associated with higher BMI (>31 compared with BMI <23 kg/m²), current or former estrogen use, current diuretic use, exercise, and higher consumption of alcoholic beverages. Overall, women with BMDs in the osteoporotic range and osteopenic range were associated with a 400% and 180% higher fracture rate, respectively, compared to women with normal BMD.

Conclusions: Results confirmed that a large percentage (~40%) of postmenopausal women in the US have previously undetected low BMD at peripheral sites and that low peripheral BMD was indicative of increased fracture risk.

Bone turnover apparently only mildly related to sex hormones in postmenopausal women

Association between endogenous hormones and sex hormone-binding globulin and bone turnover in older women: Study of Osteoporotic Fractures

Chapurlat RD, Bauer DC, Cummings SR, *Bone* 2001;29:381-387.

Background: Bone loss due to estrogen deficiency is the main determinant of osteoporosis-related fractures in postmenopausal women. Estrogen bound to sex hormone binding globulin (SHBG) is not biologically active. Few studies have examined the association between estrogen production and bone turnover. One large prospective study reported that serum estrogen and sex hormone binding globulin (SHBG) levels were predictive of subsequent risk of spine and hip fractures in postmenopausal women.

Study and Results: The relationship of estrogen, testosterone, SHBG, and biochemical markers of bone turnover were studied in 704 women enrolled in the Study of Osteoporotic Fractures. Results showed only a very weak inverse association between serum estrogen and level of bone turnover and a weak positive association between serum SHBG and bone turnover. A weak inverse association also was found between free testosterone and bone turnover.

Conclusions: Bone turnover was only mildly associated with serum concentrations of estrogen, testosterone, and SHBG in postmenopausal women. Factors other than sex hormones apparently determine bone turnover in postmenopausal women.

Common blood disorder associated with significant BMD loss in Mediterranean-area children

Bone density in the Asian thalassaemic population: a cross-sectional review

Bielinski BK, Darbyshire P, Mathers L, Boivin CM, Shaw NJ, *Acta Paediatr* 2001;90:1262-1266.

Background: Thalassaemia, a blood disease caused by a genetic mutation that affects hemoglobin synthesis, is found most commonly within populations inhabiting areas surrounding the Mediterranean. Thalassaemia is also present in certain Asian countries such as India and Pakistan. Improved survival of thalassaemic patients has increased concern over the long-term affect of the disease on the skeleton.

Study and Results: Spine BMD (DPX) was evaluated in 11 patients with thalassaemia aged 9 to 24 years. BMD was converted to an estimate of volumetric density (BMAD) using a previously published formula. All patients were shorter than expected for their age and over 70% showed significant reductions in BMD Z-scores (mean Z-score = -1.9). Z-scores were ≤ -2.5 in nearly half of all patients. BMD was still deficient after adjustment for stature (BMAD Z-score = -1.3). Mineralization deficits increased with age.

Conclusions: Skeletal problems associated with thalassaemia included growth deficits reflected in short stature, and bone mineralization deficits reflected in below normal BMD and BMAD.

Estrogens important for bone health in men

Estrogens and bone health in men

Khosla S, Melton III LJ, Riggs BL, *Calcif Tissue Int* 2001;69:189-192.

Background: Estrogen and testosterone are the major sex steroids in women and men, respectively. Recent discoveries have overturned the traditional belief that testosterone regulates bone metabolism in men. Men with rare mutations that affect estrogen function were found to have defects in skeletal metabolism that resulted in osteopenia, unfused epiphyses, and high levels of bone turnover. Estrogen treatment of these affected males led to reduced bone turnover, increased BMD, and epiphyseal fusion. These discoveries led experts to re-examine the role of estrogen in regulating bone remodeling and metabolism in adult men.

Study and Results: Subsequent studies have shown that **total** serum testosterone and estradiol (estrogen) levels do not change substantially in healthy men during aging, but the biologically active portion of this total that is not bound to sex-hormone binding globulin (SHBG), decreases to 30% to 50% of young adult levels in elderly men. Recent studies have shown that serum bioavailable estrogen predicts both the gain in BMD in young males and the loss of BMD in elderly males better than bioavailable testosterone.

Intervention studies designed to assess the relative contribution of testosterone versus estrogen therapy in preventing changes in bone formation and resorption resulting from hypogonadism found that estrogen, but not testosterone, treatment was effective. Estrogen therapy reduced bone turnover, but testosterone was ineffectual. Both testosterone and estrogen had a positive effect on osteocalcin, a marker of bone formation. **Conclusion:** Estrogen is the dominant sex hormone in regulating bone resorption in young, middle age, and elderly men. Testosterone is most responsible for the sex-related skeletal changes that occur during adolescence that result in larger bones in males. Declining, bioavailable estrogen levels appear to be substantially responsible for the decline in BMD that occurs with aging in men.

Exercise beneficial for bone in 27-year male prospective study

Bone mass and lifetime physical activity in Flemish males: a 27-year follow-up study

Delvaus K, LeFevre J, Philippaerts R, Dequeker J, Thomis M, Vanreusel B, Claessens A, Vanden Eynde B, Beunen G, Lysens R, *Med Sci Sports Exerc* 2001;1868-1875.

Background: Male osteoporosis is not well understood. Previous studies have suggested that total bone mass may be more dependent on peak bone mass in men than women. Environmental factors such as exercise and nutrition influence a person's capacity to reach the potential peak bone mass outlined by genetic factors. Exercise may have its greatest impact on bone during childhood and adolescence growth and development. Few longitudinal studies have determined whether youthful exercise translated into greater BMD in later years.

Study and Results: Measures of physical activity and lifestyle factors obtained at age 13, 18, and 40 years in a cohort of 278 male participants in a Belgian growth study were compared to BMD at the spine and total body at age 40 years. Body mass index (BMI) at any age was the most important predictor of adult BMD. BMI in childhood predicted BMI as an adult, which predicted BMD as an adult. Arm strength, running speed, and upper body muscular endurance at age 18 were predictive of BMD or BMC at age 40. Adequate calcium intake was necessary to achieve the beneficial effects of exercise.

Conclusions: Lifetime physical fitness, physical activity, and BMI were associated positively with bone mass in males at age 40.

Identification of prevalent spine deformities could lead to a decreased risk of subsequent hip fracture

Prevalent vertebral deformity predicts incident hip though not distal forearm fracture: results from the European Prospective Osteoporosis Study

Ismail AA, Cockerill W, Cooper C, Finn JD, Abendroth K, Parisi G, Banzer D, Benevolenskaya LI, Bhalla AK, Armas JB, Cannata JB, Delmas PD, Dequeker J, Dilsen G, Eastell R, Ershova O, Falch JA, Felsch B, Havelka S, Hoszowski K, Jajic I, Kragl U, Johnell O, Lopez Vaz A, Lorenc R, Lyritis G, Marchand F, Masaryk P, Matthis C, Miazgowski T, Pols HAP, Poor G, Rapado A, Raspe HH, Reid DM, Reisinger W, Janott J, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, Ambrecht G, Gowin W, Felsenberg D, Lunt M, Kanis JA, Reeve J, Silman AJ, O'Neill TW, *Osteoporos Int* 2001;12:85-90.

Background: Spine deformities/fractures recognized clinically (i.e., require medical attention) represent about one third of all vertebral deformities identified by radiographs. Clinically apparent spine deformities/fractures increase the relative risk of subsequent hip fracture by 1.8 to 3.8-fold. Even higher relative risks occur among patients requiring hospitalization. Vertebral deformities identified by radiographs increase the risk of hip fracture among elderly women, but no studies have examined their effect on subsequent limb fractures in men.

Study and Results: The ability of prevalent vertebral deformities identified from radiographs to predict subsequent limb fractures was studied in a large sample of 6344 men (mean age 64.2 years) and 6788 women (mean age 63.6 years) aged 50 years or older recruited from 29 European population centers. Subjects were followed for three years. Results showed the prevalence of vertebral deformity at baseline to be similar among men (11.7%) and women (11.8%). The relative risk (RR) of women with prevalent vertebral deformity sustaining an incident limb fracture was 1.6 (60% higher risk) compared with women without prevalent spine deformity. There was no association (RR = 1.0) of prevalent deformity with

subsequent limb fracture in men. There was a markedly increased risk of hip fracture (RR = 4.5), a mildly increased risk of other limb fractures (RR = 1.6), and no increased risk of distal forearm fractures in women with a prevalent vertebral deformity. Vertebral deformity was not associated significantly with an increased risk of hip or other limb fracture in men, although there was a nonsignificant trend toward increased fracture risk with number of deformities.

Conclusions: The risk of incident hip fracture increased dramatically in women with prevalent vertebral deformities, but there was no increased risk of distal forearm fractures. There was no association of prevalent vertebral deformity and incident limb fracture in men. Early identification of radiographic vertebral deformities associated with osteoporosis preventive therapies could potentially reduce the incidence and high costs of future hip fractures in postmenopausal women.

Osteoporosis is common among patients treated with glucocorticoids

Glucocorticoid-induced osteoporosis: Summary of a Workshop

Canalis E, Giustina A, *J Clin Endocrinol Metab* 2001;86:5681-5685.

Brief review: The regulated birth and death of bone cells is critical for normal skeletal functioning. The process of bone remodeling that couples bone formation by osteoblasts and bone resorption by osteoclasts is regulated by local and systemic factors that include glucocorticoids. The long-term skeletal changes observed in glucocorticoid-induced osteoporosis (GIO) result mainly from the effect of glucocorticoids on bone formation, although rapid bone loss that occurs shortly after initiation of glucocorticoid therapy most likely is due to increased bone resorption. Chronic glucocorticoid excess results in a decline in production and lifespan of bone forming cells that leads to a pathological decrease in their number. Bone loss is associated positively with dose and duration of therapy. A greater deleterious effect on trabecular bone compared with cortical bone results in a greater risk for fracture at the spine than at the hip. Vertebral fractures occur in 30% to 50% of patients exposed to excess glucocorticoids. Both men and women are susceptible to GIO, but postmenopausal women appear to be at the greatest risk. Bone loss is particularly profound among patients receiving glucocorticoid and immunosuppressive therapy associated with kidney, liver, and heart transplantation. Patients with rheumatological disorders are also treated frequently with glucocorticoids, and many subsequently develop osteoporosis, especially at the hip and radius, less so at the spine. BMD loss around affected joints in rheumatology patients is an early sign of disease that precedes the radiographic appearance of bone erosions. Other disorders that are treated with glucocorticoid therapy include systemic lupus erythematosus (SLE) and a variety of pulmonary diseases, including sarcoidosis. Osteoporosis is also common among patients who produce excess glucocorticoids, such as those with Cushing's syndrome. Prevention and treatment of GIO includes calcium (15 mg/d) and vitamin D (800 IU/d) to offset losses resulting from depressed intestinal calcium absorption, antiresorptive therapies such as bisphosphonates to counter accelerated bone resorption, and possibly replacement of gonadal sex hormones that are deficient frequently in GIO patients.

Smoking results in BMD loss among elderly women

Smoking and bone metabolism in elderly women

Rapuri PB, Gallagher JC, Balhorn KE, Ryschon KL, *Bone* 2001;27:429-436.

Background: Cigarette smoking is a risk factor for bone loss and osteoporosis in older men and women. A higher incidence of hip, vertebral, and forearm fractures occurs in smokers, and a recent meta-analysis reported that one in eight hip fractures was attributable to smoking.

Study and Results: The relationships among cigarette smoking, BMD, calcium-regulating hormones, calcium absorption, and bone turnover were studied in 54 smoking and 390 non-smoking elderly (aged 65-77 years) women. In addition, women who smoked less than a pack per day were compared with heavy smokers of more than a pack per day. Total body and total hip BMD were 4% and 6% lower, respectively, in heavy smokers compared with nonsmokers. A non-significant trend toward lower BMD at the spine, forearm, and femur neck, also was seen among smokers. Calcium absorption and serum vitamin D were 13% to 16% lower in heavy smokers than nonsmokers. Bone remodeling markers were increased among heavy smokers.

Conclusions: Decreased calcium absorption associated with secondary hyperparathyroidism resulted in increased bone resorption and decreased BMD among elderly women smokers.