

BMD and fracture risk - - Gender differences?

Does bone density predict fractures comparably in men and women?

Melton III LJ, Orwoll ES, Wasnich RD, *J Bone Miner Res* 2001;16:1886-1892.

Background: A recent NIH Consensus Conference concluded that the relative risk for fracture per standard deviation change in BMD is greater in women than in men, and the absolute fracture risk in men and women with the same BMD is the same. This brief review outlined the reasons why these two statements are not contradictory.

Study and Results: Numerous studies have concluded that fracture risk per SD change in BMD measured with DXA is greater in women than men. Contrary studies that found fracture risks to be equivalent between men and women used larger standard deviations for men than women, thereby confounding the comparison. Studies have reported equivalent absolute fracture risks for men and women with the same BMD, but men tended to be substantially older at an equivalent BMD, a finding that at least partially accounts for the equivalent fracture risk. Men 80 years or older experience the same BMD levels as women in their 60's. Men who fracture have higher BMD than women who fracture, but their bones are generally larger and thus their BMD adjusted for bone size is similar to or lower than that of women who fracture. Adjustment of BMD for bone size, however, does not necessarily result in a greater ability to predict fracture than BMD that is not adjusted for bone size, because larger bone size imparts a beneficial biomechanical influence on fracture risk that is recorded by areal BMD, but is ignored by measures of volumetric BMD or bone mineral apparent density (BMAD).

Conclusion: Fracture risk per 1 SD decrease in BMD is higher for women than men when the same SD is used, and the absolute risk of fracture is similar for men and women with the same BMD. Differences in age between men and women of similar BMD and biomechanical advantages of bone size appear to confound BMD measurements and influence the association of BMD and fracture risk.

Caffeine - - Associated with bone loss in elderly women

Caffeine intake increases the rate of bone loss in elderly women and interacts with vitamin D receptor genotypes

Rapuri PB, Gallagher CJ, Kinyamu HK, Ryschon KL, *Am J Clin Nutr* 2001;74:694-700.

Background: Consumption of caffeine in beverages, food, and medications is a daily occurrence in a majority of the US population. Most studies of caffeine have reported no effect on BMD, fracture rate, or calcium metabolism, but some have found increased fracture risk, decreased BMD, and negative effects on calcium metabolism. Initial reports of an association of the vitamin D receptor (VDR) polymorphism and BMD were not always confirmed by later studies, perhaps due to effects of differing environmental factors. The current study evaluated the association between caffeine intake and BMD in postmenopausal women and determined the effect that caffeine might have on the association between VDR genotype and bone loss.

Study and Results: Elderly women (n = 489) age 65-77 years were evaluated for caffeine intake and BMD (DPX) at the spine, hip, and total body. Participants were divided into low caffeine (<300 mg/d) and high caffeine (>300 mg/d) groups. Three six-ounce cups of coffee contain >300 mg of caffeine. Ninety-six women also participated in a 3-year, longitudinal component of this study. Women with high caffeine intake lost spinal BMD at a higher rate (1.9%) than subjects with low caffeine intake (1.2%). A similar, non-significant trend was seen for femoral and total body BMD. Women with a high caffeine intake and the recessive tt VDR genotype had significantly higher rates of bone loss (2.6%) at the spine than women with the TT genotype (1.4%). Bone loss was not related to VDR genotypes in women with low caffeine intake.

Conclusions: Bone loss was increased in elderly women with high caffeine intake, especially in those with the tt VDR genotype. Caffeine intake appeared to be an important dietary factor that interacted with a genetic predisposition for increased bone remodeling in elderly women.

Glucocorticoid excess - - Bad for bones and body composition in adolescent children

Glucocorticoid excess during adolescence leads to a major persistent deficit in bone mass and an increase in central body fat

Abad V, Chrousos GP, Reynolds JC, Nieman LK, Hill SC, Weinstein RS, Leong GM, *J Bone Miner Res*, 2001;16:1879-1885.

Background: Cushing's syndrome (CS) results from an overproduction of adrenal glucocorticoid hormone (cortisol), usually due to an adrenal gland tumor or overproduction of adrenocorticotrophic hormone by the pituitary gland, also usually the result of a tumor. Growth retardation, increased body fat, cessation of normal pubertal development, and decreased bone mass are among the many consequences of this disease. This is the first prospective study of the long-term results of the disease in children.

Study and Results: Identical female twins, one healthy and one afflicted with Cushing's syndrome between ages 10 and 15 years, were studied prospectively for 6 years following removal of a pituitary tumor from the affected twin. Achievement of peak bone mass, an important determinant of osteoporosis risk later in life, was severely compromised in the affected twin. BMD and estimated volumetric density (BMAD) of the CS twin was 0.7 to 3 standard deviations below her twin's values at various skeletal sites. Total body fat, especially visceral fat, had not returned to normal 6 years after the cure. Total body fat and visceral fat were 42% and 10% of total tissue mass for the CS child compared with 26% and 4%, respectively, for her normal twin.

Conclusion: Hypersecretion of adrenal cortisol during adolescence had a persistent, long-term effect on BMD and fat mass in a patient with Cushing's syndrome.

Lifestyle factors and BMD - - Interactive risk factors for vertebral deformity

The effects of lifestyle, dietary dairy intake and diabetes on bone density and vertebral deformity prevalence: The EVOS Study

Lunt M, Masaryk P, Scheidt-Nave C, Nijs J, Poor G, Pols H, Falch JA, Hammermeister G, Reid DM, Benevolenskaya L, Weber K, Cannata J, O'Neill TW, Felsenberg D, Silman AJ, Reeve J, *Osteoporos Int* 2001;12:688-698.

Background: Bone mineral density (BMD) is recognized as an important risk factor for fracture, but less is known about the way in which lifestyle and environmental factors interact with BMD to influence fracture risk. The large European Vertebral Osteoporosis Study (EVOS) of men and women aged 50 to 80 years from 36 European centers provided adequate information to evaluate the affect of lifestyle and environmental risk factors on BMD and vertebral deformity.

Study and Results: Lifestyle and dietary risk factors were graded based on responses to a questionnaire. Increased BMD was associated with increased walking, increased occupational physical activity, increased sporting activity in males, untreated non-insulin dependent diabetes, increased frequency of alcohol consumption, and increased consumption of cheese, yogurt and milk. Physical activity had a stronger effect on BMD at the hip than the spine. Lifetime smoking was associated with reduced BMD. There was a protective effect of sporting activity on BMD in men, but heavy physical activity increased the risk of deformity independent of BMD. An increased fracture risk associated with alcohol consumption was due mainly to a heightened risk associated with men who drank daily; there was no effect of alcohol on fracture risk among men who drank less often. Milk consumption before age 25 and between age 25 and 50 was weakly associated with increased BMD and reduced risk of deformity in women.

Conclusions: The risk of deformity among males was increased by heavy physical activity, decreased by sporting activity, and increased with daily alcohol consumption. The risk of deformity among women was decreased with increased milk consumption prior to age 50 years. The effects of lifestyle and environmental factors on risk of deformity appeared to be mediated mainly through their effects on BMD.

Osteoporosis and cardiovascular disease - - Indications of a potential association

Association of osteoporosis and cardiovascular disease in women with systemic lupus erythematosus
Ramsey-Goldman R, Manzi S, *Arthritis Rheum*, 2001;44:2338-2341.

Background: Several studies have suggested a connection between calcification of coronary arteries, a marker for cardiovascular disease, and osteoporosis in postmenopausal women. A similar association also may be present in women with systemic lupus erythematosus (SLE), an inflammatory, autoimmune disease occurring most often in premenopausal women. Young women (age <45 years) with SLE had a five-fold increased risk of fracture and a 50-fold greater risk of myocardial infarction compared to non-SLE women in several recent studies.

Study and Results: A pilot study evaluated carotid arteries and BMD at the lumbar spine and hip in 65 women (mean age 44.6 years) with SLE. Ultrasound was used to measure carotid plaque index and vascular wall thickness. Coronary artery calcification was measured by computed tomography in 13 of the 65 women. Results showed a significantly higher carotid plaque index in women in the lowest two tertiles for hip BMD compared with women in the highest tertile. Correlations between coronary artery calcium score and BMD at the spine and hip were also significant ($r = -0.55$ to -0.57). No differences were found in vascular wall thickness across BMD tertiles. Corticosteroid dose was similar for each tertile of BMD.

Conclusion: An inverse association between several indices of cardiovascular disease and BMD in young women with SLE was found in this small pilot study. Results supported the possibility of an association between cardiovascular disease and osteoporosis.

Quantitative ultrasound - - Bone architecture contributes small effect

Quantitative ultrasound and trabecular architecture in the human calcaneus

Nicholson PHF, Muller R, Cheng XG, Ruegsegger P, Van der Perre G, Dequeker J, Boonen S, *J Bone Miner Res* 2001;16:1886-1892.

Background: Findings from *in vitro* studies that have suggested that quantitative ultrasound (QUS) reflects trabecular bone architecture as well as density have led some to assume that QUS heel measurements provide important clinical information about bone quality. Many of these *in vitro* studies, however, have simulated conditions that are not closely similar to clinical situations. Research focused on heel QUS in human studies generally have not found evidence for significant associations between bone structure and QUS, independent of density.

Study and Results: QUS was used to examine cubes of heel cancellous bone removed from 69 cadavers. Various architectural variables and density were measured with high-resolution micro-CT. Significant associations of several architectural variables with QUS remained after adjustment for density. Multivariate regression models including architectural variables and density explained 76% to 82% of the variance of QUS, but only about 8% could be attributed to architectural variables alone. Multivariate models using architectural variables alone, however, also had good predictive ability, explaining 73% to 81% of the variance in QUS.

Conclusion: Architectural variables of cancellous bone showed significant density-independent associations with heel QUS, and combinations of architectural variables predicted QUS as well as density alone. QUS values should be viewed primarily as an indicator of bone density rather than trabecular architecture, however, until the underlying causal relationships of QUS and bone structure can be determined.

Reproductive, menstrual, and menopausal determinants of BMD

Reproductive, menstrual and menopausal factors: Which are associated with bone mineral density in early postmenopausal women

Grainge MJ, Coupland CAC, Cliffe SJ, Chilvers CED, Hosking DJ, *Osteoporos Int* 2001;12:777-787.

Background: Menstrual and menopausal factors suggested as risk factors for low BMD include early menopause, premenopausal amenorrhea, hysterectomy, and menopausal symptoms. Pregnancy and lactation cause transitory reductions in BMD, but no substantial long-term effects.

Study and Results: A sample of middle aged, healthy women (n = 580; age 45 to 61 years) not affected by disorders or medications affecting bone health answered a questionnaire on obstetric and menstrual history and were evaluated with DXA at various skeletal sites. Number of pregnancies was associated positively with BMD at the femoral neck and radius, but not the spine, or total body. Breastfeeding was not associated with BMD at any measurement site. There was a trend toward increased femoral BMD among oral contraceptive users, but overall results were not significant. Women who used oral contraceptives at an early age, however, showed significantly higher BMD at the radius and total body sites, and positive trends at other sites. There was a positive association between years of menstruation and BMD at most measurement sites. Women with hysterectomies had a higher BMD at all sites than women with an intact uterus, presumably because of their subsequent use of hormone replacement therapy (HRT). Duration of menopausal symptoms was associated with lower BMD at the total body and forearm sites.

Conclusions: HRT and years of menstruation were important predictors of increased BMD. Duration of menopausal hot flushes showed a small negative association with BMD. The importance of oral contraceptives and hysterectomy as predictors of BMD requires further study.

Weight loss - - A risk factor for hip fracture

Weight loss from maximum body weight among middle-aged and older white women and the risk of hip fracture: the NHANES I Epidemiologic Follow-up Study

Langlois JA, Mussolino ME, Visser M, Looker AC, Harris T, Madans J, *Osteoporos Int* 2001;12:763-768

Background: Body weight is an important determinant of BMD. Weight loss increases bone loss and increases fracture risk. Studies have shown repeatedly that weight loss in elderly women increases the risk of hip fracture, but few studies have evaluated increased risk of hip fracture among middle age women who lose weight.

Study and Results: Women (n = 2410) aged 50 to 74 years from the NHANES I study were followed for 22 years to determine the relationship of change of weight to risk of hip fracture. A 10% or greater loss of weight from maximum body weight was associated with a 2.5-fold greater risk for hip fracture in middle-aged women and a 2.0-fold increased risk in elderly women. Weight loss in the elderly presumably increased fracture risk through its association with reduced bone mass, decreased muscle strength, increased disability, and increased risk of falling. Weight loss in middle-aged women most likely resulted from dieting, rather than from poor health or chronic disease.

Conclusion: Weight loss of 10% or more from maximum weight was an important risk factor for hip fracture among middle-aged and elderly women.

BMD improved following liver transplantation

Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study

Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, Fagioli S, Naccarato R, Luisetto G, *Osteoporos Int* 2001;12:749-754

Background: Abnormalities in bone development (osteodystrophy) are common in patients with end-stage liver disease. Men with severe liver disease often have reduced gonadal function (hypogonadism), a condition that contributes to the high prevalence of osteoporosis associated with liver disease.

Study and Results: Bone metabolism and gonadal function were studied in 23 consecutive males (mean age 48 years) evaluated for liver transplantation. More than half (52%) of the patients had T-scores in the osteoporotic range (<-2.5) at baseline. Additional BMD loss during the first three months following transplantation probably was related to the effects of steroid therapy and immobilization on bone. Serum vitamin D levels and bone formation returned to normal 12 months after transplantation. BMD increased significantly at 12 and 24 months post-transplantation.

Conclusions: Osteoporosis was present in a majority of men with end-stage liver disease, but gonadal function recovered three months after transplantation, followed by a steady increase in BMD at 6, 12, and 24 months post-transplantation.

BMD - - Potential marker for verbal memory function in the elderly

Bone mineral density and verbal memory impairment – Third National Health and Nutrition Examination Survey

Zhang Y, Seshadri S, Ellison RC, Heeren T, Felson DT, *Am J Epidemiol* 2001;154:795-802

Background: Research has shown that estrogen has beneficial effects on brain physiology in areas that are important to memory function. Studies that have measured the relationship of circulating estrogen or hormone replacement therapy (HRT) to memory and other brain functions, however, have shown mixed results. Lifetime estrogen exposure would be a more appropriate measure to determine whether an association between estrogen and cognitive function exists, but lifetime exposure is difficult to measure. BMD might serve as an important marker for lifetime estrogen exposure. Estrogen has been shown to be an important determinant of BMD in both men and women. Several recent studies have suggested that BMD might serve as a useful marker for cumulative estrogen exposure and risk of breast cancer. Women with high BMD, indicative of a high lifetime exposure to estrogen have a significantly increased risk of breast cancer compared to women with low BMD. A similar relationship might hold among BMD, lifetime estrogen exposure, and memory function.

Study and Results: Data from the Third National Health and Nutrition Examination Survey (NHANES III) were used to compare BMD with verbal memory impairment, a strong predictor of the future development of dementia. Results from 4,304 subjects aged 60 years or older showed that the prevalence of verbal impairment decreased with increased femoral neck BMD in both men and women. Verbal memory impairment was only 64%, 65% and 44% as likely for subjects in the upper three quartiles of BMD, respectively, as for subjects in the lowest quartile of femur neck BMD. Results were similar for other femur measurement sites.

Conclusions: There was an inverse association between femur BMD and verbal memory impairment among elderly subjects. BMD could be considered a marker for lifetime estrogen exposure and a predictor for verbal memory function in the elderly.

Body composition - - Influences factors that affect BMD

Determinants of bone mineral density in older men and women: body composition as mediator

Pluijm SMF, Visser M, Smit JH, Popp-Snijders C, Roos JC, Lips P, *J Bone Miner Res* 2001;16:2142-2151.

Background: Body composition is one of several factors that have been shown to influence BMD. Other influential determinants of BMD include nutrition, genetics, lifestyle, disease, medication, and hormonal factors. This study examined the direct and indirect influence of various determinants on BMD and body composition.

Study and Results: Men and women (n = 522) aged 55-85 years participating in the Longitudinal Aging Study Amsterdam (LASA), were evaluated over a 12-year period for body composition and numerous factors known to influence total hip BMD. Appendicular muscle mass and fat mass were examined as body composition factors that could potentially act as mediators between other determinants and BMD. Increased body weight and daily walking were positively associated with hip BMD in women, while age and high sex hormone binding globulin (SHBG) levels were associated with lower BMD. Participation in sporting activities was associated with higher BMD in males, and age, smoking, and high PTH levels were associated with lower BMD. Fat mass and muscle mass independently had a positive relationship to BMD in both men and women. Fat mass, but not muscle mass, influenced the effect of weight change, walking activity, and SHBG on hip BMD in women. Neither fat mass nor muscle mass appeared to play a mediating role between determinants and BMD in men.

Conclusions: Fat mass and muscle mass were strong predictors of BMD in both men and women. Fat mass influenced the association of weight change, walking activity, and SHBG with hip BMD in women.

DXA hand BMD - - Useful for assessing progression of rheumatoid arthritis

Relationship between bone mineral density and radiologic scores of hands in rheumatoid arthritis

Ardicoglu O, Ozgocmen S, Kamanli A, Pekcutucu I, *J Clin Densitometry*, 2001;4:263-269

Background: Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that affects the synovial membranes that line the cartilage surrounding freely moving joints. The progress of the disease is measured frequently by a combination of radiographic and clinical findings that result in a score that describes the extent of the pathological change in the cartilage and underlying bone. Radiographs, however, provide a relatively inaccurate and imprecise measure of bone loss around an affected joint. Dual energy x-ray absorptiometry (DXA) provides a more accurate, precise, and sensitive method to evaluate bone loss in the hands of RA patients.

Study and Results: Bone mineral density (BMD) of the hand and spine measured with DXA (DPX) was compared with hand radiographs scored according to five different methods designed to assess the course of RA. The advantages of hand BMD over radiographs include a) lower radiation risk, b) better precision, c) ability to detect early disease before radiographical evidence is apparent, d) elimination of observer bias, and e) accurate measurement of periarticular osteoporosis. The short-term precision of hand BMD was 0.8%. Radiologic scoring took from 3 to 10 minutes, depending upon the method used. Hand measurements with DXA took about 10 minutes. Hand BMD, but not spine BMD, was associated with duration of disease ($r = -0.4$).

Conclusions: Hand BMD was sensitive to joint changes and correlated with disease duration. Authors noted that results "...indicate that hand BMD measurements may be as useful in assessing the course of rheumatoid arthritis as radiologic scoring methods."

Hyperthyroid treatment associated with reduced BMD 10 years after the cure

Bone mass after long-term euthyroidism in former hyperthyroid women treated with ¹³¹Iodine.

Serraclara A, Jodar E, Sarabia F, Hawkins F, *J Clin Densitometry* 2001;4:249-255

Background: Hyperthyroidism has a negative effect on bone turnover that leads to reduced BMD and increased risk of fracture. Radioiodine therapy for hyperthyroidism leads to normalization of thyroid function in many women, but less is known of BMD and fracture risk.

Study and Results: Women ($n = 26$) with a minimum of four years of normal thyroid function following radioiodine treatment for Graves' disease or toxic nodular goiter were evaluated with DXA and various biochemical measures of bone turnover. BMD at the spine, femur neck and Ward's triangle were significantly lower in treated women than in normal controls after a mean period of 10 years of sustained normal thyroid function. Women who were menopausal or postmenopausal at the time of therapy had the greatest reductions in BMD.

Conclusions: The recovery of BMD was not complete even after long-term normal thyroid function in previously hyperthyroid women treated with radioiodine therapy.

Oral contraceptives - - Associated with reduced BMD in premenopausal women

Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study.

Prior JC, Kirkland SA, Joseph L, Kreiger N, Murray TM, Hanley DA, Adachi JD, Vigna YM, Berger C, Blondeau L, Jackson SA, Tenenhouse A, for the CaMOS Research Group, *Can Med Assoc* 2001;165:1023-1029

Background: Studies of the effect of oral contraceptives (OC) on BMD and fracture risk have been somewhat controversial. Most studies of oral contraceptive use in perimenopausal women and past use in menopausal women have indicated a positive effect on BMD. Studies of premenopausal women generally have found either no effect or a small positive effect of OC on BMD, but several found a higher risk of fracture in premenopausal OC users.

Study and Results: The aim of this study was to determine whether oral contraceptive use in premenopausal women aged 25-45 years was associated with BMD at the spine and proximal femur. Users of OCs (past or present) did not differ generally from non-users in age at menarche, calcium intake, vitamin D supplementation, BMI, and years of education, but users reported greater use of alcohol and more pack-years of smoking than those who never used OCs. BMD was numerically lower in OC users compared with non-users at all spine and femur measurement sites. BMD was significantly lower in OC users at the lumbar spine and trochanter sites, after adjustment for age, BMI, and height. Further adjustment for smoking, alcohol intake, and weight cycling (loss and regain of more than 10 lbs) led to additional differences between OC users and nonusers at the femoral neck and Ward's sites. Adjusted BMD differences of 2.4% at the femoral neck and 4.3% at the trochanter suggested a 20% to 30% increased fracture risk among premenopausal OC users compared with nonusers. Previous reports of a beneficial effect of OCs on BMD were based mainly on retrospective studies of menopausal women that might have been confounded by the association of OC use with ovarian hormone therapy, a treatment that is well known to increase BMD.

Conclusions: Oral contraceptive use was associated with reduced BMD at the lumbar spine and femur trochanter in 500+ premenopausal women participating in a national, Canadian, population-based study.

Pregnancy and lactation - - Differing effects on cortical and trabecular bone

The effects of pregnancy and lactation on bone mineral density

More C, Bettembuk P, Bhattoa HP, Balogh A, *Osteoporos Int* 2001;12:732-737

Background: Calcium requirements of pregnancy and lactation that are not met by calcium ingestion are met by calcium from the maternal skeleton. Numerous articles have reported loss of maternal bone mineral during lactation, but studies of BMD loss and increased fracture risk in pregnant and lactating women have been inconclusive.

Study and Results: BMD (DPX) was evaluated prospectively in 38 women during the first three months of their first pregnancy and for 12 months after delivery. BMD decreased during pregnancy at both trabecular (lumbar spine and ultradistal radius) and cortical (distal radius) measurement sites. Women who lactated for less than a month showed a BMD recovery at trabecular sites by 6 months and at the cortical distal radius site by 12 months following delivery. Women who breastfed for 1 to 6 months showed a continuous loss of BMD at trabecular sites during lactation, followed by an increase in BMD that did not reach baseline values at 12 months postpartum. Women who breastfed for more than 6 months had declines in spine BMD throughout the lactation period. Cortical BMD increased and returned to normal by 12 months in all three lactation groups

Conclusions: There was significant loss of BMD at both cortical and trabecular sites during pregnancy. Lactation appeared to have its greatest effect on BMD at trabecular bone sites.

Prostate cancer treatment increases fracture risk

Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer.

Oefelein MG, Ricchuiti V, Conrad W, Seftel A, Bodner D, Goldman H, Resnick M, *J Urol* 2001;166:1724-1728

Background: Clinicians have known for more than 30 years that androgenic hormones stimulate prostate cancer. Suppression of these hormones is the standard treatment for prostate cancer. Androgen suppression, however, leads to bone loss and increased risk of osteoporosis. Few studies have examined the effect of androgen suppression and other risk factors for fracture in males with prostate cancer.

Study and Results: Skeletal fractures occurred in 4% and 20% of 181 consecutive patients with prostate cancer treated with androgen-suppressive therapy for 5 and 10 years, respectively. Fracture was related significantly to length of suppressive therapy. The greatest fracture risk occurred with slender white males. Black race and increased body mass index were protective against fracture.

Conclusions: Prostate cancer patients treated with androgen-suppressive therapy had a 5-fold greater risk of hip and other skeletal fractures when compared with men of similar age. Length of therapy was an important determinant of fracture risk.

Anorexic women may be at high risk of osteoporosis

Osteoporosis in eating disorders: a follow-up study of patients with anorexia and bulimia nervosa

Zipfel S, Seibel MJ, Lowe B, Beumont PJ, Kasperk C, Herzog W, *J Clin Endocrinol Metab* 2001;86:5227-5233

Background: Eating disorders are associated with considerable morbidity in industrialized countries. Anorexia nervosa (AN), a psychophysiological condition usually seen in young women, is characterized by a prolonged refusal to eat that results in emaciation, amenorrhea, emotional disturbance concerning body image, and other biological changes. Bulimia nervosa (BN) is an eating disorder characterized by bingeing and purging behavior. A previous study found that women with long-term AN (average 5.8 years) had markedly deficient BMD (DPX) levels and a fracture rate seven-fold higher than healthy age-matched women. Osteoporotic fractures occurred in 44% of subjects whose long-term outcome was categorized as poor.

Study and Results: Women with anorexia nervosa (AN) or bulimia nervosa (BN) were studied prospectively over a 3.6-year follow-up period. Women with AN had a low percentage of body fat (mean = 6.4%) and were markedly underweight. The prevalence of osteopenia increased from 34.8% for women anorexic for 3 years to 54.2% for women anorexic for 7 years. Osteoporosis was found in 13.0% and 20.8% of subjects at the three-year and 7-year intervals, respectively. Biochemical bone markers showed increased bone resorption among anorexic patients. Anorexic women with a binge eating/purging subtype had the greatest risk for developing osteoporosis. Spine BMD was lost at an annual rate of 3.7% among non-recovering anorexic women. A subgroup of recovering women showed improvements in weight and slight, but not significant, increases in spine BMD. All but one bulimic patient had BMD within the normal range.

Conclusions: Women with anorexia, particularly those with the binge/purging subtype, had a high risk of osteoporosis and an increased need for bone-protective therapy.

BMD may influence clinical decision making in patients with adrenal incidentalomas

Bone loss rate in adrenal incidentalomas: A longitudinal study

Chiodini I, Torlontano M, Carnevale V, Guglielmi G, Cammisa M, Trischitta V, Scillitani A, *J Clin Endocrinol Metab* 2001;86:5337-5341

Background: Adrenal incidentalomas (AI) are adrenal masses detected incidentally during abdominal imaging for some other medical condition. The increased frequency of abdominal imaging has led to increased discovery of these small tumors that show no overt clinical symptoms. Patients often show some increase in cortisol secretion, however, a condition known as subclinical hypercortisolism (SH). Determination of skeletal involvement in AI could influence clinical management of AI patients.

Study and Results: Spine and femur BMDs were evaluated in 24 female patients with adrenal incidentalomas at baseline and after 29.6 months. Patients were divided into two groups based on urinary cortisol secretion. Results showed that the rate of spinal bone loss was significantly higher in the group with the highest mean urinary cortisol levels. Femur neck BMD showed a similar, but non-significant trend. Additionally, urinary cortisol secretion and BMD were correlated when all subjects were grouped together.

Conclusions: Adrenal incidentaloma patients with high cortisol secretion have higher bone loss than those with lower secretion. Authors concluded that spinal BMD was necessary for good clinical treatment decision-making.

” Based on these results, the need for BMD evaluation at the spine in all female AI patients is strongly suggested. In fact the knowledge of reduced bone mass may help in making decisions about the need for surgical excision of AI tumors smaller than 4 cm.”

Leptin appears to influence bone quality in postmenopausal women

Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women

Yamauchi M, Sugimoto T, Yamaguchi T, Nakaoka D, Kanzawa M, Yano S, Ozuru R, Sugishita T, Chihara K, *Clin Endocrinol* 2001;55:342-347

Background: Weight and total body fat mass are important determinants of BMD in postmenopausal women. BMD is influenced favorably by increased mechanical loading that occurs with increased weight, and from the conversion of androgens to estrogen that occurs in the adipose (fat) tissue of postmenopausal women. Leptin, a hormone produced by the obese gene (ob), is formed in white fatty tissue and secreted into the circulation. Leptin works in a classic feedback mechanism by binding to a receptor in the hypothalamus and causing a decrease in fat mass by suppressing appetite and increasing energy consumption. Recent studies have suggested that leptin also might have a direct effect on bone cells and might stimulate bone formation.

Study and Results: Leptin concentration, percentage fat mass (%fat), and BMD were assessed in 39 postmenopausal women evaluated for osteoporosis. Results showed a significant positive relationship between circulating leptin levels and %fat ($r = 0.56$). Leptin also was mildly, but significantly associated with BMD at the spine ($r = 0.23$), femoral neck ($r = 0.29$), one-third radius ($r = 0.17$), and total body ($r = 0.18$). Leptin was positively associated with BMD even when age and %fat were taken into account, but %fat was not associated with BMD when adjustment was made for leptin concentration. Leptin levels were significantly lower in women with vertebral fractures than those without, regardless of %fat concentrations.

Conclusions: Leptin might play some role in maintaining bone quantity and quality in postmenopausal women.

Leptin may be related to BMD in healthy men

Association between serum leptin concentrations and bone mineral density, and biochemical markers of bone turnover in adult men

Sato M, Takeda N, Sarui H, Takami R, Takami K, Hayashi M, Sasaki A, Kawachi S, Yoshino K, Yasuda K, *J Clin Endocrinol Metab* 2001;86:5273-5276.

Background: Leptin, a newly discovered hormone, is controlled by the ob gene and secreted mainly by fat cells. Leptin influences brain centers (hypothalamus) that control appetite and energy metabolism through classic feedback mechanisms. Leptin deficiency or faulty leptin receptors in the brain might be the cause of certain forms of obesity. Studies on mice have indicated that leptin may also affect BMD.

Study and Results: The correlation between serum leptin concentration, calcaneus BMD, and biochemical markers of bone turnover were studied in 221 Japanese men. Serum leptin levels were associated strongly with body weight ($r = 0.48$), body mass index ($r = 0.57$), and total fat mass (0.60). BMD was positively associated with fat mass with no adjustment for weight, but was negatively associated with fat mass after weight adjustment. Similarly, BMD for the lowest tertile of leptin concentration was higher than that for the highest tertile after adjustment for body weight. Results appeared to contradict the well-known finding of increased BMD in obese subjects, who usually have increased leptin concentrations. Leptin was associated with reduced bone formation and decreased BMD in adult men. Other studies have found that obese individuals might be resistant to leptin. Leptin resistance might contribute, along with higher mechanical loading, to the protective effect of obesity on BMD.

Conclusions: Serum leptin concentrations were inversely related to bone formation and BMD in healthy, adult men.

Phytoestrogens have beneficial effects on bone in postmenopausal women

High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women

Mei J, Yeung SSC, Kung AWC, *J Clin Endocrinol Metab* 2001;86:5217-5221

Background: The incidence of hip fractures is increasing at an alarming rate in Asian countries. Hip fracture incidence has tripled during the last 30 years in southern China, according to a recent study. Population demographics indicate that half of the world's hip fractures will occur in Asia by the year 2050. Cultural biases against hormone-replacement therapies indicate that nonhormonal therapies might be the treatment of choice for many postmenopausal Asian women. Phytoestrogens, plant-derived compounds that are structurally similar to estrogens and have weak estrogenic effects on bone, might be an acceptable alternative therapy. A significant portion of the Asian diet consists of foods containing soybeans or soy products that are high in phytoestrogen.

Study and Results: Habitual intake of dietary phytoestrogen was determined by food-frequency questionnaire in 650 Chinese women aged 19 to 86 years. Postmenopausal women in the highest tertile of phytoestrogen intake had higher BMD than women in the lowest tertile. Significant BMD effects were seen mainly at trabecular bone sites, but all spine and femur sites showed trends for increased BMD with higher phytoestrogen intake in postmenopausal women. Women generally show increased bone turnover associated with the normal decline in estrogen production following menopause. A decrease in biochemical bone markers among Chinese women with high phytoestrogen intake, however, indicated that the BMD increase was probably related to decreased bone turnover. Phytoestrogen intake was not associated with BMD in premenopausal women.

Conclusions: Dietary phytoestrogen intake was associated with increased BMD at the spine and hip in postmenopausal women. Dietary phytoestrogens might slow down or reverse the increase in bone turnover that follows the decline in estrogen at the menopause.

Rheumatoid arthritis is a major risk factor for hip fracture

Threefold increased risk of hip fractures with rheumatoid arthritis in Central Finland

Huusko TM, Korpela M, Karppi P, Avikainen V, Kautianen H, Sulkava R, *Ann Rheum Dis* 2001;60:521-522

Background: Rheumatoid arthritis (RA) is a well-known risk factor for hip fracture, but the extent of the association is not well appreciated.

Study and Results: All hip fracture patients admitted to a Finnish hospital between 1991 and 1993 were evaluated for presence of rheumatoid arthritis. Rheumatoid arthritis was three times more likely to be present in hip fracture patients than in age- and sex-matched controls. Nearly 6% of women with hip fracture also had RA. Corticosteroid use and lack of physical activity are common in this disease and are potential contributing factors to the association of RA with hip fracture.

Conclusions: Patients with rheumatoid arthritis have a markedly increased risk of hip fracture.

Vertebral fractures are associated with a diminished quality of life

The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis

Silverman SL, Minshall ME, Shen W, Harper KD, Xie S, on behalf of the Health-related Quality of Life Subgroup of the Multiple Outcomes of Raloxifene Evaluation Study, *Arthritis Rheum*, 2001;44:2611-2619

Background: Vertebral fracture, the most common osteoporotic fracture, is associated with decreased physical functioning and psychological well-being, and back pain. Health-related quality of life (HRQOL), an assessment tool that quantifies aspects of physical, social, emotional, and functional health was used in the Multiple Outcomes of Raloxifene Evaluation (MORE) study that examined the long-term effects of raloxifene on the skeleton in postmenopausal women with T-scores indicative of osteoporosis.

Study and Results: Women from the MORE trial (n = 1395, mean age 68.5 yrs) were evaluated with HRQOL at baseline and annually for three years. Women with prevalent fractures had lower HRQOL scores than women without a prevalent fracture. Scores were lower for each subsequent fracture. Fractures in the L1-L4 vertebral region had the greatest effect on HRQOL, particularly the physical function component. Incident fractures affected physical functioning, clinical symptoms, and emotional well-being.

Health-related quality of life was not affected by the presence of adjacent vertebral fractures. Prevalent vertebral fractures increased the risk for subsequent vertebral fracture.

Conclusions: Both prevalent and incident vertebral fractures were associated with a decline in HRQOL. Prevalent fractures lower in the vertebral column had a greater negative effect on HRQOL than fractures higher in the spine.

BMD and fracture are good predictors of mortality and morbidity in men

Mortality, morbidity, and assessment of fracture risk in male osteoporosis

Johnell O, Kanis J, Gullberg G, *Calcif Tissue Int* 2001;69:182-184.

Review: Fractures result in increased mortality in both sexes, but several large studies have shown that mortality related to most clinical fractures is higher in men than women. The DUBBO study from Australia, found that the standardized mortality ratio was 2.18 for women with fractures and 3.17 for men with fractures, compared to similar subjects with no fracture. Similar differences were seen for most other major fractures. Higher mortality in men with osteoporotic fractures was associated with a higher frequency of associated diseases (comorbidity). Other studies have shown that BMD is a good predictor of death in both men and women. In fact, BMD has been found to be a better predictor of death than blood pressure and cholesterol in both men and women. Risk factors for fracture tend to be similar for both sexes. Important risk factors include body mass index, recreational and physical activity, comorbidity, and secondary osteoporosis. Men and women with prior fractures have about double the risk for a subsequent fracture. New studies are needed to determine the BMD threshold at which osteoporosis is diagnosed and treated in men.

BMD not reduced by low-dose methotrexate treatment of rheumatology patients

The effect of low dose methotrexate on bone density

Cranney AB, McKendry RJ, Wells GA, Ooi DS, Kanigsberg ND, Kraag GR, Smith G, *J Rheumatol*, 2001;28:2395-2399.

Background: Methotrexate is associated with bone loss at the relatively high doses required for cancer treatment. Methotrexate has been used recently at lower doses to treat disorders such as rheumatoid arthritis and psoriasis. The effect of long-term, low-dose methotrexate on BMD has not been well documented.

Study and Results: Approximately 60 patients with rheumatoid arthritis (RA) and 60 patients with psoriasis/psoriatic arthritis (Ps/PsA) were subdivided into groups that were either treated or not treated with methotrexate. Results showed there were no significant differences in femoral neck, trochanter, or radius BMD (DPX) between patients with RA or Ps/PsA and controls. BMD was significantly higher than controls in RA patients treated with methotrexate, but not in Ps/PsA patients. There were no significant differences in Z-scores at any measurement site between patients treated with and without methotrexate. A possible limitation of the study was that most patients were receiving lower doses of methotrexate than is now common in clinical practice.

Conclusion: Low-dose methotrexate did not have a negative effect on BMD in patients with rheumatoid arthritis or psoriasis.

DXA demonstrates that bisphosphonates diminish bone loss following lung transplantation

Prevention of bone loss and fracture after lung transplantation

Cahill BC, O'Rourke MK, Parker S, Stringham JC, Karwande SV, Knecht TP, *Transplantation*, 2001;72:1251-1255.

Background: Osteoporotic fractures and BMD loss are common problems associated with lung transplantation. Immunosuppressive medications that induce high bone turnover appear to be involved in

the 15 to 18% fracture rate and 4% to 12% loss of BMD reported during the first year following lung transplantation.

Study and Results: Lung transplant patients who underwent osteoporosis evaluation with DXA and treatment with a bisphosphonate starting before or after transplantation were assessed for fracture one year after transplantation. Osteopenia or osteoporosis was present in most patients and 29% had sustained one or more vertebral compression fractures prior to transplantation. New fractures occurred in only 4% of subjects and spine and hip BMD remained stable or improved in 65% and 86% of patients one year after transplantation. Most patients who lost BMD had begun bisphosphonate treatment only after transplantation.

Conclusion: Aggressive antiresorptive treatment with bisphosphonates decreased fracture rate and maintained or improved BMD 1 year after lung transplantation.

DXA demonstrates that bisphosphonate reduces bone resorption around femoral implants

Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty: a prospective randomized study

Venesmaa PK, Kroger HPJ, Miettinen HJA, Jurvelin JS, Suomalainen OT, Alhava EM, *J Bone Miner Res*, 2001;2126-2131.

Background: The long-term success of total hip arthroplasty (THA) is related directly to the quality of bone surrounding the femoral implant. Implantation of a stiff femoral prosthesis results in reduced weight bearing (stress shielding) followed by increased resorption in non-stressed areas of the surrounding (periprosthetic) bone. Specialized DXA software allows measurement of changes in BMD in bone surrounding an implant. Periprosthetic bone loss of from 16% to 30% has been reported in previous studies. Bone resorption around the implant leads to stem loosening and loss of functionality that may require implant replacement. Some implant manufacturers have considered BMD results when designing implants to minimize the amount of bone loss due to 'stress shielding'. Bisphosphonates might prolong the life of an implant by minimizing bone resorption in the bone adjacent to the implant.

Study and Results: A series of 13 patients receiving uncemented, primary THA were randomized to receive either alendronate (10 mg/d) and calcium (500 mg/d) or calcium (500 mg/d) alone for six months following implantation. BMD loss (0.9%) in the upper femur (Gruen zones 1+7) in the alendronate-treated group was much less than BMD loss (17.1%) in the calcium-only treatment group. BMD loss in the total periprosthetic area (Gruen zones 1 through 7) was 2.6% in the alendronate group and 9.9% in the calcium-only group. Results suggested that alendronate might increase implant survival times by decreasing the amount of bone resorption surrounding the implant. A study with a much longer follow-up time is necessary to verify this hypothesis.

Conclusion: Alendronate led to significantly less periprosthetic bone loss after uncemented THA compared with patients without bisphosphonate therapy.

Physicians missing opportunity to diagnose and treat osteoporosis in patients who present with hip or wrist fracture

Missing a therapeutic window of opportunity: an audit of patients attending a tertiary teaching hospital with potentially osteoporotic hip and wrist fractures

Smith MD, Ross W, Ahern MJ, *J Rheumatol*, 2001;28:2504-2508.

Background: Osteoporosis is a silent disease often not evident until the occurrence of a non-traumatic fracture. BMD is a well-accepted surrogate marker for bone quality and bone strength that should be used to diagnose osteoporosis in patients who seek treatment for potentially osteoporotic hip and wrist fractures.

Study and Results: All patients (n = 218) between age 40 and 85 years who were admitted to a teaching hospital with a hip fracture or seen in an emergency department with a wrist fracture over a specified period were included in the study. Eighty-four percent of patients reported receiving no information about osteoporosis at the time of fracture. BMD was measured subsequently in only 32% of patients, and 38% were offered some osteoporosis treatment. Factors most likely to result in a BMD evaluation were female

sex, history of a previous fracture after age 50, family history of osteoporosis, or the use of concurrent medications that posed a potential risk for osteoporosis. Main predictors for treatment for osteoporosis were age, abnormal BMD, history of fracture after age 50, and history of a minimal-trauma fracture. Calcium supplementation was the major treatment offered.

Conclusion: The majority of patients with potential osteoporotic fractures were not evaluated or treated for osteoporosis. Health providers should improve their awareness of the possibility of osteoporosis and implement evaluation procedures (DXA) to ensure diagnosis and treatment of fracture patients with osteoporosis.

Regular assessment of BMD recommended for women with affective disorders who are treated with thyroid hormone

Bone mineral density in pre- and post-menopausal women with affective disorder treated with long-term L-thyroxine augmentation

Gyulai L, Bauer M, Garcia-Espana F, Hierholzer J, Baumgartner A, Berghofer A, Whybrow PC, *J Affect Disord*, 2001;66:185-191.

Background: Patients with affective disorders such as manic-depressive psychosis often receive, in addition to other medications, doses of thyroid hormone (thyroxine) sufficient to suppress secretion of thyroid stimulating hormone (TSH). Suppressing TSH treatment has been shown by some studies to result in bone loss, while others have found no negative skeletal effects. The current study extended previous work on the effect of suppressive thyroxine therapy on bone in psychiatrically ill patients.

Study and Results: An equal number (n = 13) of premenopausal and postmenopausal patients being treated with thyroxine for bipolar disorder or major depression were evaluated for BMD (DPX) at the spine and femoral neck. Z-scores for spine and hip BMD for both pre- and postmenopausal women did not differ from the reference range standards for the combined groups, but a higher-than-expected number of postmenopausal women had Z-scores that were more than one standard deviation below reference standards.

Conclusion: Adjuvant thyroxine therapy did not result in a clinically significant decrease in BMD among all women treated for affective disorders, but a higher than expected number of treated, postmenopausal women had low BMD. Authors noted... "This study underscores the need for regular assessment of BMD during adjunctive thyroid treatments for affective disorder, especially among postmenopausal women."

Secondary osteoporosis is common in men

Secondary causes of osteoporosis in men

Compston J, *Calcif Tissue Int* 2001;69:193-195.

Review: Male osteoporosis can be categorized as primary, secondary, or age-related. Primary osteoporosis in men is poorly defined. The distinction between secondary osteoporosis and risk factors for osteoporosis is often unclear. Risk factors may contribute indirectly to secondary osteoporosis by affecting associated factors such as body weight, physical activity, and balance. Approximately 30% of male osteoporosis can be attributed to secondary causes such as glucocorticoid excess, hypogonadism, alcohol abuse, organ transplantation, gastrointestinal disease, malignancy, medications, cigarette smoking, and genetic disorders. Hip fractures occur generally in elderly men with disorders that result in reduced body mass index, glucocorticoid therapy, reduced neuromuscular and cognitive function that increase the risk of falling, and/or reduced physical activity. Obesity has been shown to be protective of fracture in men, as it has in women. Clinical management of secondary osteoporosis should include treatment for the underlying diseases where possible. Bisphosphonates have been shown in some studies to preserve BMD and reduce the incidence of vertebral fractures in men receiving glucocorticoid therapy, but large variations in the number of fractures in untreated men receiving glucocorticoids have led to uncertainty about the precise recommendation for bisphosphonate therapy. Studies are needed to establish the efficacy of bisphosphonates in reducing non-vertebral fracture risk in glucocorticoid-treated men.