

Clinical Risk Factors

Acute and long-term increase in fracture risk after hospitalization for stroke

Kanis J, Oden A, Johnell O. *Stroke* 2001; 32:702-706.

Background: The risk of hip fracture increases from two to four-fold following a stroke, and most often occurs after a fall to the side of the body affected by the stroke.

Study and Results: A study of Swedish medical records covering the time between 1987 and 1996 found 273,288 patients hospitalized for stroke. The incidence of all fractures increased seven-fold in the year following the stroke, with a greater than 4-fold increase in hip fracture. Duration of hospital stay was associated with fracture risk in men, suggesting that length of immobility and presence of other illnesses influenced fracture incidence. The younger the stroke patient, the higher the relative risk of fracture, an indication that fracture risk was related especially to the stroke in younger patients who would not ordinarily be prime fracture candidates. Stroke patients should be especially targeted for anti-fracture treatment, including hip protectors, exercises to decrease the chances of falls, and pharmaceutical intervention.

Conclusion: Stroke patients have a high fracture risk and should be treated aggressively to prevent fractures.

Relevance: This and several other recent papers emphasize the need to adequately diagnose and treat skeletal deficiencies in stroke patients.

Bone mineral density in adolescent females with recently diagnosed anorexia nervosa

Wong JCH, Lewindon P, Mortimer R, Shepard R. *Int J Eat Disord* 2001;29:11-16.

Background: Anorexia nervosa (AN) is a severe eating disorder associated with bone loss and fractures that mainly affects adolescent females.

Study and Results: Twenty-four recently diagnosed anorexic patients (age 8-16 years) were evaluated with DEXA (DPX, Lunar). Results showed no significant loss of total body BMD and a minor, non-significant change in lumbar spine BMD. Lean body mass was associated positively with bone, explaining over 65% of the variance of BMC and BMD.

Conclusion: Early and aggressive intervention within the first year of diagnosis may prevent the loss of BMD associated with anorexia nervosa of longer duration.

Relevance: DEXA and body composition provide clinically useful measures of the effect of anorexia nervosa on bone and body composition compartments prior to and during treatment.

DXA – Menopausal Bone Loss

Bone loss in relation to menopause: a prospective study during 16 years

Ahlborg HG, Johnell O, Nilsson BE, Jeppsson S, Rannevik G, Karlsson MK. *Bone* 2001;28:327-331.

Background: Most studies showing accelerated bone loss following menopause have been cross-sectional. Few studies have evaluated bone loss at the menopause in a prospective study design.

Study and Results: Bone loss measured by single photon absorptiometry at the radius was evaluated in a group of women (n=125) who were followed from age 48 to age 64 years. BMD at age 48 years showed moderate correlation with BMD at age 64 years ($r = 0.4 - 0.5$). BMD loss was greater during the first five years (2.4%/year) following menopause than during the last 6 years (0.4%/year), irrespective of age. There was no correlation between age at menopause and BMD at age 64 years.

Conclusion: Women with low BMD prior to menopause also had low BMD at age 64 years. Most loss of BMD occurred during the 5 years immediately following menopause.

DXA – Primate Studies

A nonhuman primate model of age-related bone loss: a longitudinal study in male and premenopausal female rhesus monkeys

Black A, Tilmont EM, Handy AM, Scott WW, Shapses SA, Ingram DK, Roth GS, Lane MA. *Bone* 2001; 28:295-302.

Background: Age-related bone loss begins during the third to fourth decade for both men and women. Additional bone loss related to hormonal changes, especially estrogen depletion in women, begins at the menopause. Rhesus monkeys housed in several large research facilities around the country provide a model for studying age-related bone loss longitudinally.

Study and Results: DEXA (DPX, Lunar) was used to study BMD in 20 premenopausal rhesus monkeys over a four-year period. Both males and females showed an age-related decline at the forearm, and total body BMD declined in older females with a similar trend in males. None of the monkeys in this study were considered menopausal. Lean body mass was associated with BMD at all sites in males, a finding in agreement with human studies. An apparent increase in spine BMD associated with severity of osteoarthritis agreed with results from human studies.

Conclusion: Rhesus monkeys exhibit age-related declines in bone that mirror those of humans, and provide a useful model for studying age-related changes in the human skeleton.

DXA - Therapy

Effects of clodronate on vertebral fracture risk in osteoporosis: a 1-year interim analysis

Mccloskey E, Selby P, De Takats D, Davies BM, Robinson J, Francis R, Adams J, Pande K, Beneton M, Jalava T, Loyttyniemi E, Kanis JA. *Bone* 2001;28:310-315.

Background: Drugs tested in clinical trials as potential therapies to prevent or treat osteoporosis must show efficacy in reducing vertebral fracture risk. Clodronate, a bisphosphonate (1600 mg/day) shown to be effective in reducing fracture risk in patients losing bone due to cancer, was studied to determine whether a smaller dose (800 mg/day) might be effective in reducing fracture risk in osteoporotic patients.

Study and Results: Osteoporotic men and women (T-score <-2.5 for women and <-3 for men) with at least one vertebral fracture were recruited to participate in a 3-year study of clodronate (800 mg/day). First year preliminary results showed that BMD at the spine and hip increased (1-3%) with therapy, but declined with placebo. Fractures were half as frequent in the clodronate group compared with placebo.

Conclusion: Clodronate (800 mg/day) was effective in preventing bone loss and showed a positive trend toward a decreased risk of vertebral fracture.

DXA – Total Body

Bone mineral density during reduction, maintenance and regain of body weight in premenopausal obese women

Fogelholm GM, Sievanen HT, Kukkonen-Harjula TK, Pasanen ME. *Osteoporosis Int* 2001;12:199-206.

Background: Body weight and bone mass are closely related; high body weight is associated with increased BMC and BMD. Loss of excess body weight through weight-reduction programs benefits the body in many ways, but may lead to loss of total body BMD.

Study and Results: Obese women who participated in a three-month weight reduction program, followed by nine months of walking intervention, were followed up for an additional 24 months. Weight change throughout the study showed a significant correlation with change in radial, trochanteric, and total body BMD (XR-26, Norland). Initial losses of BMD were reversed when weight was regained. Possible explanations included: a) decreased mechanical loading due to less body weight, b) changes in energy

balance associated with changes in the bioavailability of estrogen, c) malnutrition, including a lack of dietary calcium, d) artifacts of DXA scanning related to changes in bone edge detection that lead to apparent increases in bone area and decreases in BMD with weight loss.

Conclusion: BMD loss associated with weight loss was small, reversible and of little clinical significance. Authors suggested that some of the BMD change associated with weight loss might be a technological artifact.

Fracture Prediction – Possible Importance of LVA

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, Bruges Armas J, Cannata JB, Delmas PD, Dequeker J, Dilson 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. *Osteoporosis Int* 2001; 12:85-90.

Background: Subjects with a vertebral deformity have an increased risk for subsequent vertebral deformities. Few studies have investigated whether subjects with a vertebral deformity have an increased risk of hip or forearm fractures.

Study and Results: Spinal radiographic data on over 6000 men and nearly 7000 women aged 50 years old or older were collected from over 31 European centers. Among 391 women who sustained a limb fracture during follow-up, a prevalent vertebral deformity was a strong predictor of hip fracture (relative risk 4.5), but only a weak predictor (RR = 1.6) of other limb fractures, and not predictive of forearm fracture. A prevalent vertebral deformity was not predictive of limb fractures in men.

Conclusion: Prevalent vertebral fractures are strongly predictive of hip fracture in women.

Relevance: LVA should prove to be an important tool to detect vertebral deformity and thus provide an important indication of future risk of hip fracture in women.

Acute and long-term increase in fracture risk after hospitalization for vertebral fracture

Johnell O, Oden A, Caullin F, Kanis JA. 2001;12:207-214.

Background: Vertebral fracture is a signal indicator of osteoporosis. Subjects with vertebral fracture have a higher risk of future fracture at the spine and other skeletal sites. This paper assesses the magnitude of that risk.

Study and Results: Swedish medical records for the period between 1987 and 1994 were used to find all patients admitted to a hospital for vertebral fracture. Over 17,000 patients admitted for spine fractures resulting from low-energy trauma were followed over the next 2 to 8 years. The risk of any fracture increased 4 to 6-fold in the very elderly (age 85 years or more), but the fracture risk ratio (30-50 fold increased risk) was much higher in younger men and women (age 50-54) admitted for vertebral fracture, relative to the general population. Fracture risk was particularly high during the 6 months immediately following a fracture and decreased by 75% over the subsequent four-year period. A similar, but less intense, pattern was seen for hip fracture. The risk ratio for hip fracture for young men and women age 50-54 years admitted for vertebral fracture was 17 to 20 compared with a risk ratio of about 3 for the oldest subjects (age 85 to 89 years).

Conclusion: Fracture risks were as high in men as in women with vertebral fractures. All patients with vertebral fracture should be offered treatment, regardless of whether bone densitometry is performed. Short-term therapy may lessen the acute fracture risk that occurs during the first year following a vertebral fracture.

Lifetime and five-year age-specific risks of first and subsequent osteoporotic fractures in postmenopausal women

Doherty DA, Sanders KM, Kotowicz MA, Prince RL. *Osteoporosis Int* 2001;12:16-23.

Background: Knowledge of lifetime fracture incidence and five-year age-specific fracture risks provide important information to national health agencies and others interested in assessing the burden of osteoporosis.

Study and Results: Fracture risk was assessed in 109,923 individuals over age 35 years participating in the Geelong Osteoporosis Study in Australia. A statistical model (Markov process with Monte Carlo simulations) was used to estimate age-specific fracture rates with increasing age. Results showed that 42% of women aged 50 years or older will sustain at least one osteoporotic fracture in their lifetime. The lifetime risks of a hip, spine or other fracture were 17%, 9.6%, and 30.4%, respectively. Only 1.9% of women will have sustained their first fragility fracture before age 55, but 49.1% of women over age 89 will have sustained an osteoporotic fracture. Over the next 5 years only 2.8% of women under age 55 would be expected to fracture, compared with 61.6% for women over 89 years. The lifetime risk of hip fracture in Australia (17%) was similar to the risk reported for the USA and the UK (14% - 18%).

Conclusion: The burden of osteoporotic fracture found in Australia mirrors the burden of fracture found in other industrialized countries.

Peripheral DXA

Ability of peripheral DXA measurements of the forearm to predict low axial bone mineral density at menopause

Pouilles JM, Tremollieres FA, Martinez S, Delsol M, Ribot C. *Osteoporosis Int* 2001;12:71-76.

Background: Studies have proven that BMD at axial sites is the gold standard for diagnosing osteoporosis. Forearm measurements have been proposed as a prescreening tool to identify subjects who should be followed up with axial scans.

Study and Results: Early postmenopausal women (n = 234) attending a menopause clinic were scanned at peripheral sites (proximal and distal radius and ulna) with pDXA (Norland) and at axial sites (spine and femur) with DPX (Lunar). The WHO classification of osteopenia (T-score ≤ -1) and osteoporosis (T-score ≤ -2.5) was used to measure agreement between peripheral and axial measurements. Peripheral measurements showed moderate correlation with axial sites (r = 0.4 to 0.6), with a somewhat better spine correlation (r = 0.53 to 0.60) than femur (r = 0.39 to 0.47). Spine and femur BMD identified 17.5% as osteoporotic, compared with 14% at the proximal forearm and 3.4% at the distal forearm. However, only 39% of subjects identified as osteoporotic at the forearm were also osteoporotic at the spine or hip. A high percentage (57% to 59%) of women who were normal at peripheral sites were osteopenic at axial sites. The pDXA cutoff values for the forearm that allowed identification of 95% of women osteoporotic at axial sites was -0.7 . Guidelines that suggest a T-score of <-1 at the forearm for intervention would have missed about 50% of women who were either osteoporotic or osteopenic at axial sites.

Conclusion: Peripheral DXA did a reasonably good job of identifying women osteoporotic at axial sites, but was less able to identify women with osteopenia at axial sites.

Ultrasound – Achilles

Quantitative ultrasound of bone and markers of bone turnover in Cushing's syndrome

Cortet B, Cortet C, Blanckaert F, d'Herbomez M, Marchandise X, Wemeau J-L, Decoux M, Dewailly D. *Osteoporosis Int* 2001; 12:117-123.

Background: Cushing's syndrome results from an excess production of corticosteroids from the adrenal gland, usually caused by excess production of adrenocorticotrophic hormone from the pituitary gland. An excess of corticosteroids, either given as a drug or through abnormally high endogenous production, accounts for most cases of secondary osteoporosis and up to 25% of all cases of osteoporosis overall.

Study and Results: Twenty-five patients with Cushing's syndrome were evaluated with quantitative ultrasound (ACHILLES, Lunar) at the heel, DEXA at the spine and femoral neck, and bone markers. QUS was shown to be a useful in discriminating patients with Cushing's syndrome from controls. BUA and Stiffness were 7.6% and 10.6% lower in patients than controls. However, unlike previous studies that showed that decreases in QUS and BMD were similar, decrease of lumbar spine BMD was nearly twice as

large as that seen for QUS. Most bone markers were not significantly different between patients and controls.

Conclusion: QUS was found to be useful in evaluating bone in patients with Cushing's syndrome, but was somewhat less sensitive than spine BMD in this study.

Ultrasound – Bone Structure

Is quantitative ultrasound dependent on bone structure?

Njeh CF, Fuerst T, Diessel E, Genant HK (2001) A reflection. *Osteoporosis Int* 2001; 12:1-15.

Review: Studies have suggested that quantitative ultrasound (QUS) may provide information on bone structure not provided by measures of BMD, and thus may improve the estimate of bone strength and fracture risk. An exhaustive review of the evidence that ultrasound attenuation is due to structural features of bone and that these features are related to bone density and strength was presented. Evidence shows that QUS is influenced by biomechanical material properties, is highly correlated to density within the relevant clinical range, and is a good predictor of bone strength at a diagnostic level similar to that of BMD and, therefore, provides a useful prediction of fracture risk. Clinical benefits of QUS combined with BMD have not been proven conclusively to be additive. Additive benefits may await technological changes providing greater accuracy and precision.