

Osteoporosis and MS

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Workshop Agenda

- Incidence, risk factors and medical management of osteoporosis in MS patients
- Pathophysiology of osteoporosis and effects of IFN in bone homeostasis
- Diagnostic procedures and hormonal influence on bone health
- Evidence supporting exercise and rehabilitation in osteoporosis

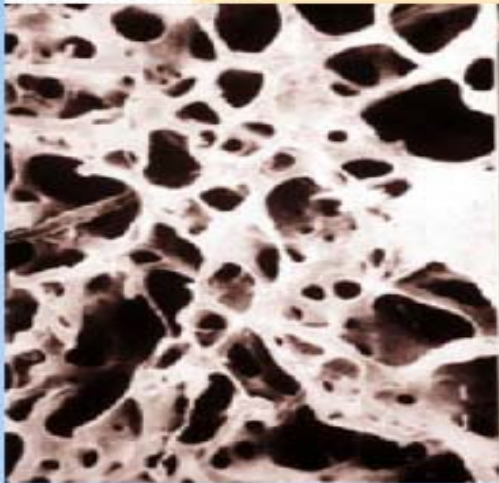
Osteoporosis

- A skeletal disease characterized by:
 - Low bone mass and
 - Microarchitectural deterioration of bone tissue
- Leads to bone fragility with increased fracture risk.
- Affects one in every two women over the age of 50
- About 10 million Americans suffer from osteoporosis and an additional 34 million have an increased risk for the disease.

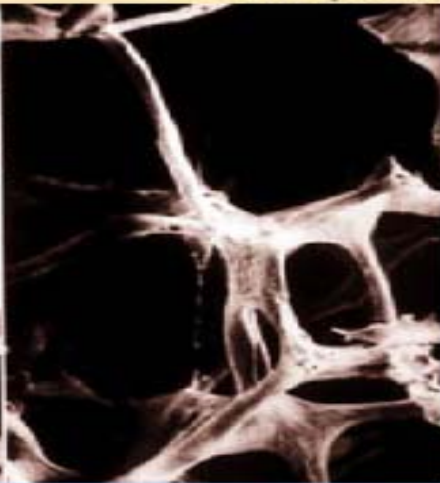
Osteoporosis

What is osteoporosis?

Normal Bone



Osteoporosis



Vertebrae

Hip

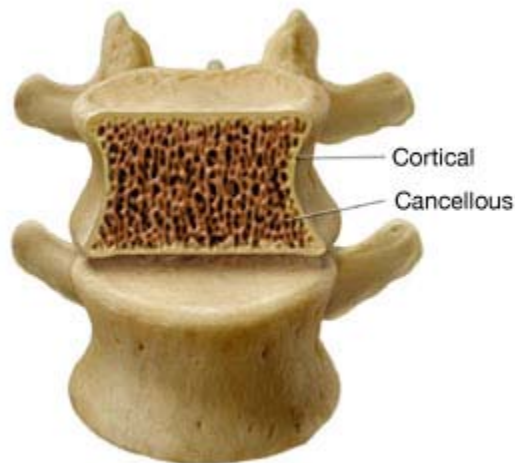
Wrist

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Osteoporosis

- The definition given by The World Health Organization is based on bone mineral density (BMD) results obtained on DEXA scans
- **Osteoporosis** is defined as a BMD value that is -2.5 SD or more below the mean of a young adult of the same sex (T-score). A value of -1 to -2.5 SD is called **osteopenia**.

Osteoporosis



- Normal cortical bone forms a compact shell around the more delicate cancellous bone.
- During the accelerated period of bone loss immediately after menopause, cancellous bone loss increases 3-fold, while rates of cortical bone loss are slower.

Osteoporosis

- Bones go through well coordinated cycles in which old bone is broken down (resorption) and new bone is produced (formation)
- Specific bone cells are involved in this process:
 - the osteoblast is involved in bone formation and
 - the osteoclast is involved in bone resorption.
- Between the ages of 20-30 bone mass usually peaks: bone is formed faster than it is broken down.
- After age 30 the ratio between the two processes shifts and bone resorption increases substantially
- During acute, life-threatening illnesses as well as in chronic illnesses there is a negative balance favoring resorption, resulting in decreased bone mass

Signs and Symptoms

- Osteoporosis is often called a "silent disease" because there can be no symptoms.
- Some signs include:
 - back pain
 - loss of height
 - curvature of the back ("dowager's hump"), and
 - fractures usually of the back (vertebral), hip, or wrist.

Diagnosis of Osteoporosis

- Physical assessment
- Identification of risk factors
- Bone mineral density testing.

Risk Factors for Osteoporosis and Fractures

- Low Bone Mineral Density (low BMD or T score)
- Age: menopause and andropause
- Previous low trauma fractures
- Low body weight (BMI)
- Smoking
- High alcohol intake (> 2 Units/day)
- Family history of osteoporosis and fractures

Medical Conditions with Increased Risk for Osteoporosis

- Endocrine abnormalities: hyperthyroidism, hyperparathyroidism, diabetes, hypercortisolism
- Chronic use of steroids
 - Other medications: i.e AED
- Malnutrition: calcium, Vit D and/or protein/calorie deficiency, TPN
- Rheumatoid arthritis
- Malignancies
- **Multiple Sclerosis**

MS and Osteoporosis

- MS patients are particularly susceptible to low BMD
- Cross sectional studies have shown that the prevalence of osteopenia and osteoporosis in men and women with MS is nearly 80-85% [Weinstock-Guttman, Multiple sclerosis 2004; Cosman F, Neurology 1999].
- A prospective study (over 2 years) showed MS patients are losing substantially more bone in the femoral neck than controls (Cosman F, 1999)
 - 3% and 6% loss per year in pre- and postmenopausal women with MS versus 0.5% and 0.8% per year in controls
 - 7.3% loss per year in men with MS versus vs. 1.6% loss in controls.
 - Bone loss in the spine was also greater in women with MS than in controls (1.6 to 3.5% per year loss in MS patients vs. no change in controls).

Osteoporosis in men

- Osteoporosis and the increased fracture risk become apparent in men approximately 10 years later than women.
- However approximately 20% of healthy men in the age range 55-64 years were found to be osteopenic.
- Emerging data suggest a significantly increased prevalence of osteoporosis in men with MS compared to age-matched controls
- 80% of our men MS patients had a reduced bone mass of either lumbar spine or the femoral neck: of these 42.5% had osteopenia and 37.5% had osteoporosis (Weinstock-Guttman, 2004)

MS and osteoporosis

- “Low bone density is the rule, not the exception in MS patients and its deleterious effects are particularly stark in post-menopausal patients and male patients over 40 years old”.

Weinstock-Guttman & Murali Ramanathan, 2004



University at Buffalo
The State University of New York

The Institute for MS Neuroscience



Bone Fractures and MS

- Osteoporosis has the potential to exacerbate the physical limitations imposed by MS
- MS patients are particularly susceptible to falls that can more easily cause fractures if patients have low BMD.
- Fractures unrelated to major trauma occur in 22% of MS patients compared to 2% of controls: a 11-fold increase in fracture risk [Weinstock, 2004; Cosman, 1998].

Vertebral Fractures

- Although vertebral fractures are perceived as more benign than the hip fractures, they are associated with restrictive lung disease with reduced vital capacity
- On average, each vertebral fracture is considered to reduce the pulmonary vital capacity by 9%. [Schlaich, 1998].
- These fractures can also run the risk of numerous comorbidities including infection, blood clots, pneumonia, and death.

MS and Osteoporosis

- The causes of low BMD in MS are probably multi-factorial:
 - Immobilization caused by physical disability
 - Glucocorticoids used for treatment of relapses.
 - Vitamin D deficiency
 - Overall result of the chronic inflammatory disease process

EDSS and Osteoporosis

- Multivariate linear regression analysis indicated that the neurological disability measured by EDSS ($P < 0.0001$) as well as BMI ($P = 0.0004$) were the important factors associated with low femoral BMD (Weinstock, 2004; Zorzon 2005)
- EDSS was the important factor ($P = 0.0017$) associated with low BMD at the lumbar spine in men (Weinstock-Guttman, 2004) but less evident in women with MS (Ozcosmen S, J Bone Miner Metab 2005)

Vitamin D

- Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death.
- The major function of vitamin D is to maintain calcium homeostasis.
 - It accomplishes this by increasing the efficiency of dietary calcium intestinal absorption.
 - In case of inadequate dietary calcium intake vitamin D is signaling to osteoclast precursors to mature and dissolve the calcium stored in the bone.

Vitamin D

- Vitamin D is metabolized in the liver and then in the kidney to active 1,25-dihydroxyvitamin D [1,25(OH)(2)D].
- 1,25(OH)(2)D receptors (VDR) are present not only in the intestine and bone, but in a wide variety of other tissues, including the brain, heart, stomach, pancreas, activated T and B lymphocytes, skin, gonads, etc.
- Vitamin D deficiency is a major unrecognized health problem. Not only does it cause rickets in children, osteomalacia and osteoporosis in adults, but may have long lasting effects.
- Vitamin D deficiency may have serious adverse consequences, including:
 - increased risk of hypertension
 - cancers of the colon, prostate, breast, and ovary,
 - type 1 diabetes and
 - multiple sclerosis.

Vitamin D and Osteoporosis

- MS patients have significantly lower vitamin D levels (17.3 ng/ml vs 43.1 ng/ml; $P < 0.001$) compared to controls
 - 61% had a serum level less than 20 ng/ml (Ozcosmen S, J Bone Miner Metab. 2005;23(4):309-13.)
- Low levels of 25-hydroxy-vitamin-D were seen in 37.5% of our patients. No clear correlation to decreased bone mass was shown. (weinstock-Guttman, 2004)
- Bone loss in the spine occurred faster in MS patients with low (<20 ng/mL) 25-hydroxyvitamin D levels (1.9% per year, $p < 0.04$) compared with MS patients with normal levels (Cosman F, 1999)
- At the femoral neck, bone loss was substantial in all patients, but was somewhat faster in the group with low levels of 25-hydroxyvitamin D
- Vitamin D repletion in MS patients who are deficient might reduce, the rate of bone loss and decrease osteoporosis-related fractures. (Cosman F, Neurology, 1999)

Steroids, MS and Osteoporosis

- Continuous steroid treatment beyond 5 months was found as a predictor for increased bone loss (Cossman, Neurology 1999).
- No clear association between IV steroid therapy and BMD was evident in the multivariate analysis in our group (Weinstock-Guttman, 2004).
- Similarly treatment with repeated high dose IV MP pulses was not associated with osteoporosis in patients with MS who participated in a trial of IVMP (Zivadinov, Neurology 2001).
 - Osteopenia was observed more frequently in MS patients than healthy controls.
 - Osteopenia was found only in patients treated for relapses, who had a significantly higher EDSS score than patients in the high dose MP group (Zorzon, J Eur Neurol 2005).

Steroids, MS and Osteoporosis

- 30 acutely relapsing patients with MS were given 1000 mg of IVMP daily for 3 days followed by an oral prednisone taper for 2 weeks (Schwid, SR Arch. Neurol 1996)
- Prior to treatment, bone density in patients with MS was already reduced at the femoral neck compared with an age-matched reference population, but the degree of this reduction did not correlate with prior steroid exposure.
- Lumbar density, was normal and following the steroid pulse, lumbar bone density increased, becoming 1.7% greater than baseline 6 months later ($P = .02$).
- Femoral bone density did not change on average, but the patients who required a cane or walker for ambulation had a 1.6% decrease in femoral bone density, while those with better ambulation had a 2.9% increase ($P = .04$).
- A single corticosteroid pulse did not reduce bone density in fully ambulatory patients with MS and multiple pulses did not have a cumulative effect on bone

Steroids, MS and Osteoporosis

- 13 MS patients receiving IVMP 15 mg/kg daily for 10 d were studied with DEXA and calcaneal quantitative ultrasonometry at baseline and 6 months after therapy (Dovio AJ Clin Endocrinol Metab. 2004).
- Bone turnover markers including: serum osteocalcin (OC), aminoterminal propeptide of type I collagen (PINP), bone isoform of alkaline phosphatase (bALP), carboxyterminal telopeptide of type I collagen (CTX), and urinary calcium/creatinine ratio (uCa/Cr) were obtained during the 10-d cycle and 3 months later.

Steroids, MS and Osteoporosis

- An immediate, impressive fall of OC and PINP (-80 +/- 3 and -54 +/- 5% at d 2, respectively), which persisted throughout the whole treatment period ($P < 0.0001$ for both markers).
- bALP levels showed only a modest decrease at d 6 (-19 +/- 7%, $P < 0.05$), with subsequent return to baseline in d 7-10.
- After 3 months, OC, PINP, and bALP levels rose to +51 +/- 22, +37 +/- 16 (NS), and +61 +/- 17% ($P < 0.01$) with respect to baseline, respectively.
- Although high-dose, short-term IVSM regimens cause an immediate decrease in bone formation with a transient increase of bone resorption, the discontinuation of such regimens is followed by a high bone turnover phase
- No change in quantitative ultrasonometry parameters and BMD was observed 6 months after therapy (Dovio AJ Clin Endocrinol Metab. 2004).

MS and Osteoporosis

- Is osteoporosis thought to be related to MS disease itself?
- The next talk is summarizing the strong link between the immune system and bone homeostasis suggesting that osteoporosis in MS is related to multiple factors including the inflammatory disease process itself.
- Disease control can decrease the risk for bone loss.

MS and Osteoporosis

- A recent survey of 220 women with MS revealed that 50% do not get regular medical preventive checkups (Shabas D, Weinreb H, 2000).
- 85% have never had bone density testing, 50% are not taking calcium supplements, and 71% are not taking vitamin D.
- Among the postmenopausal sample, 81% have never had bone density testing, 50% are not taking calcium supplements

Osteoporosis Therapy in MS Patients

- The therapeutic approach for osteoporosis in MS patients should be similar to the approach for treating osteoporosis in general population.
- The therapy of osteoporosis requires a complex intervention that includes:
 - Medications
 - Vitamin supplementation
 - Exposure to sunlight and
 - Physical therapy

Therapy of Osteoporosis in MS patients

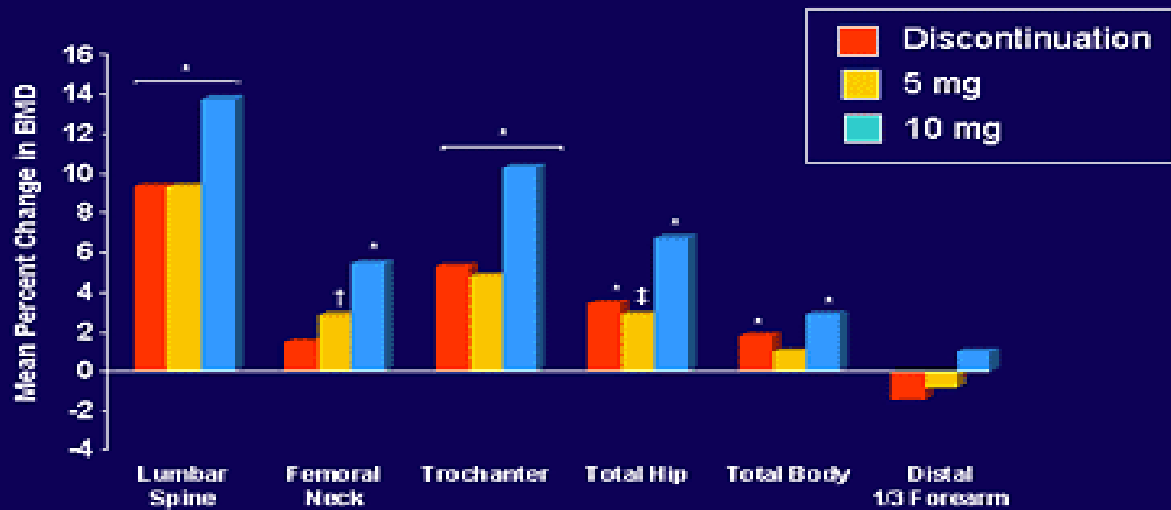
- Overview of medical interventions
 - Bisphosphonates
 - Alendronate
 - Risedronate
 - Ibandronate
 - Calcitonine
 - Hormone Replacement therapy
 - Raloxifen
 - Anabolic agents, parathormone
 - RANKL antibody

Osteoporosis Therapy in MS

- Bisphosphonates are effective agents for reducing vertebral and nonvertebral fracture risk.
- These medications are used to slow bone breakdown and increase bone density.
- In major clinical trials these products were shown to reduce vertebral fracture risk to a similar degree, approximately 40-50% after 3 or 4 years.
- The therapy also significantly decreased the nonvertebral fracture risk as well as reversed bone loss that has already occurred.
- However, the changes in BMD predicted only 11-17% of the decrease in fracture risk leaving most of the risk reduction unexplained.

Long term therapy

10-Year Alendronate: Mean Percent Change in BMD, Baseline to Year 10

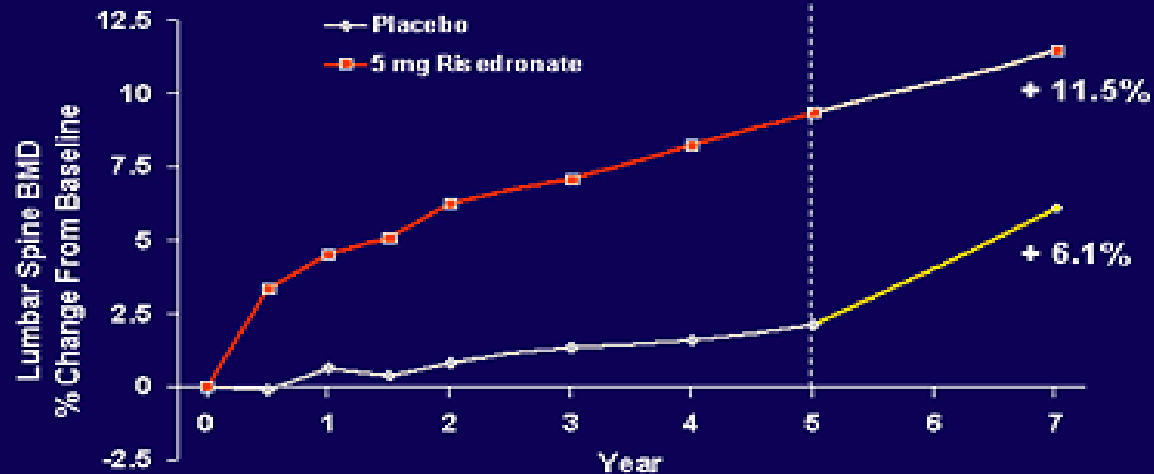


* $P < .001$; † $P < .01$; ‡ $P < .05$; (within-treatment test of mean percent change=0 for the specified intervals).

Bone H, et al. *N Engl J Med*. 2004;350:1189-1199.

Long term therapy

Long-Term Effect of Risedronate Therapy

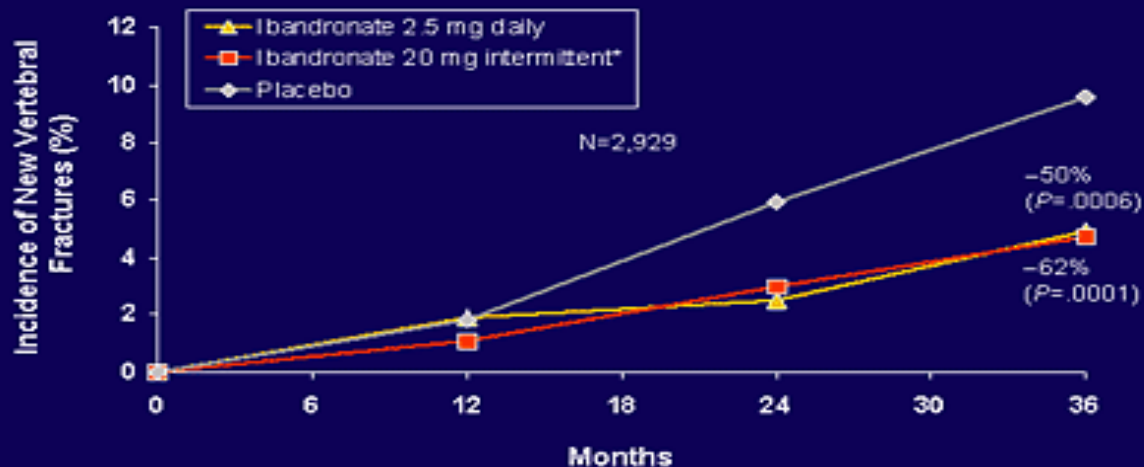


P < .05.

Goemaere S, et al. *J Bone Miner Res.* 2003;19(suppl 1):SA-346.

Ibandronate Therapy

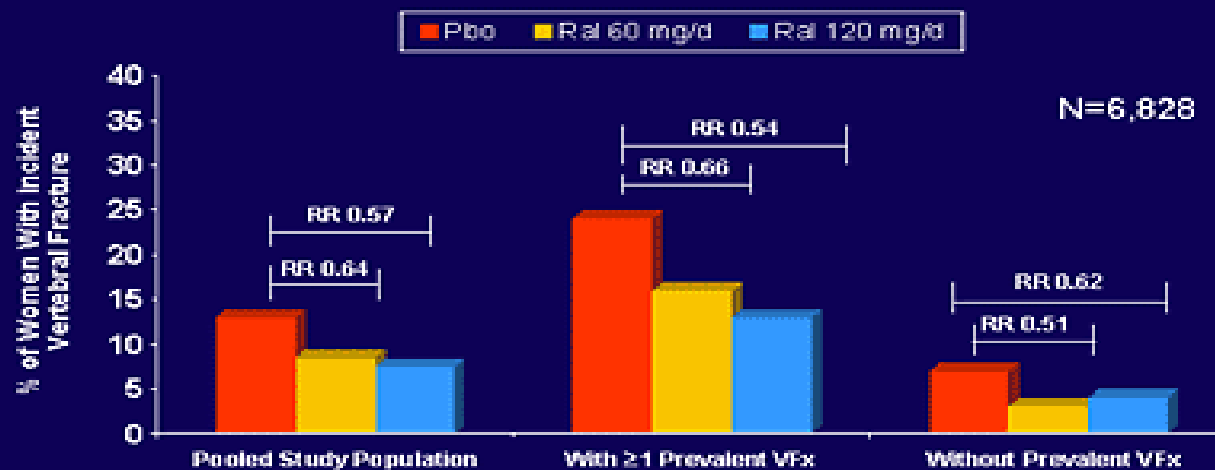
BONE Study: Incidence of New Vertebral Fractures Daily and Intermittent Oral Ibandronate



*20 mg every other day for 12 doses every 3 months.
Chesnut CH III, et al. *J Bone Miner Res.* 2004;19:1241-1249.

Estrogen Receptor Modulators Raloxifene

Effect of Raloxifene on Vertebral Fractures After 4 Years of Treatment (MORE Trial)

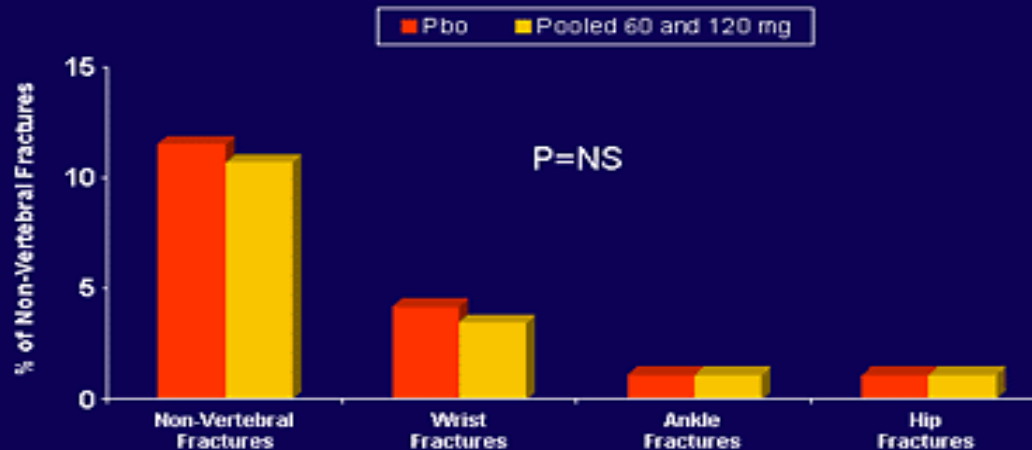


Cumulative proportion of women with at least one incident vertebral fracture at 4 years. RR in patients with or without a prevalent vertebral fracture.

Delmas PD, et al. *J Clin Endocrinol Metab.* 2002;87:3609-3617.

Estrogen Receptor Modulators Raloxifene

Effect of Raloxifene on Non-Vertebral Fractures After 4 Years of Treatment (MORE Trial)



Delmas PD, et al. *J Clin Endocrinol Metab.* 2002;87:3609-3617.

Hormone Therapy

- Hormone therapy can be taken orally or via a skin patch.
- It has been shown to slow bone loss in women after menopause.
- However, because the increased risk for stroke and myocardial infarction found in post-menopausal women during the pivotal hormone replacement therapy trial, HRT are recommended only for severe menopausal symptoms such as non controlled "hot flushes".

Calcitonin

- Salmon calcitonin nasal spray at a dose of 200IU daily was shown to significantly reduce the risk of new vertebral fractures in postmenopausal women with osteoporosis. (Am J Med.2000;109:267–276).
- Prolonged administration of parenteral calcitonin, by injections of 100 IU every 1 or 2 days, can prevent postmenopausal or postovariectomy bone loss, and is also able to increase trabecular bone mass
- Bone pain is the most common symptom in osteoporotic patients.
 - To date, there is mounting evidence that calcitonin significantly reduces bone pain in osteoporosis, and that the analgesic effect can be evident as soon as the second week of treatment.
 - No available data for MS patients.

Human Parathyroid Hormone

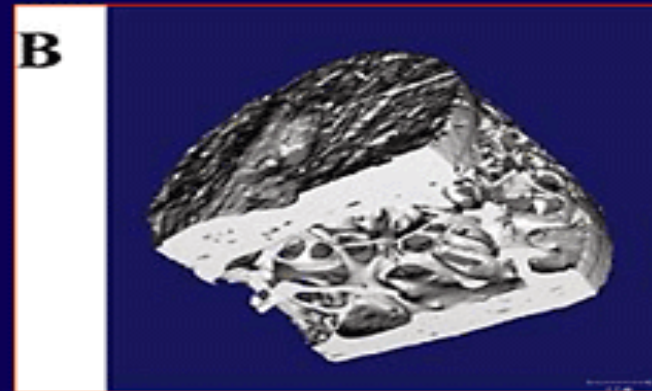
- Recombinant PTH is the only anabolic agent currently approved for the treatment of osteoporosis.
- PTH stimulates bone formation, in contrast to antiresorptive agents, which reduce bone resorption and formation.
- Recent investigations involving the PTH(1-34) and PTH(1-84) peptides showed that:
 - ❑ Adding a bisphosphonate to PTH in previously untreated individuals does not produce additional bone benefit
 - ❑ However, sequential use of PTH followed-up by an antiresorptive agent is highly effective at increasing BMD.
 - ❑ Adding PTH after an antiresorptive agent also produces substantial bone density increments
 - ❑ PTH can repair underlying micro-architectural defects in bone and improve bone mass substantially.

Parathyroid Hormone

Human Parathyroid Hormone (1–34) [Teriparatide] and Bone Structure



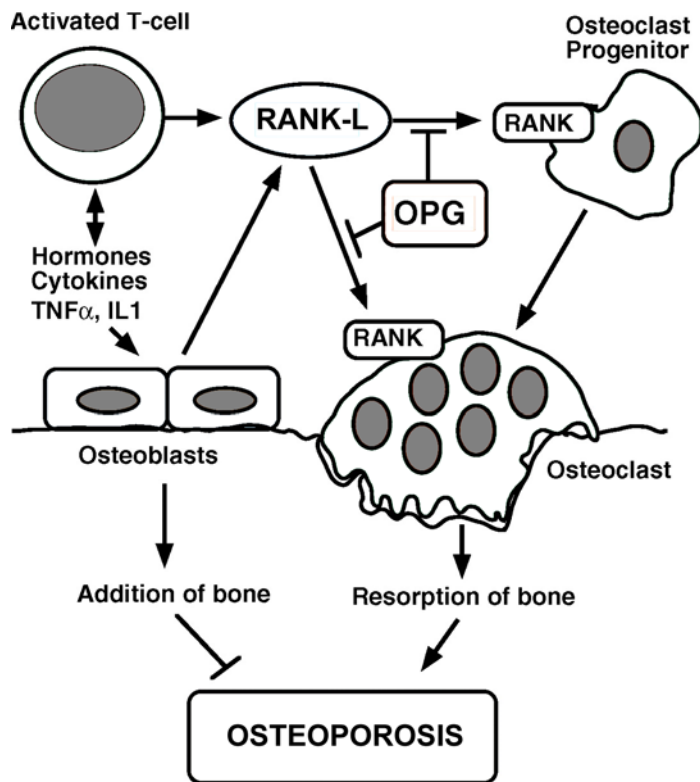
Baseline



21 Months of Treatment

Jiang Y, et al. *J Bone Miner Res.* 2003;18:1932-1941.

RANK-RANKL-OPG



- Receptor activator of nuclear factor- κ B ligand (RANKL) is essential for osteoclast differentiation, activation, and survival.
- The fully human monoclonal antibody denosumab (formerly known as AMG 162) binds RANKL with high affinity and specificity and inhibits RANKL action (Michael R. McClung, N Eng J Med, 2006)

RANKL- Ab (Denosumab)

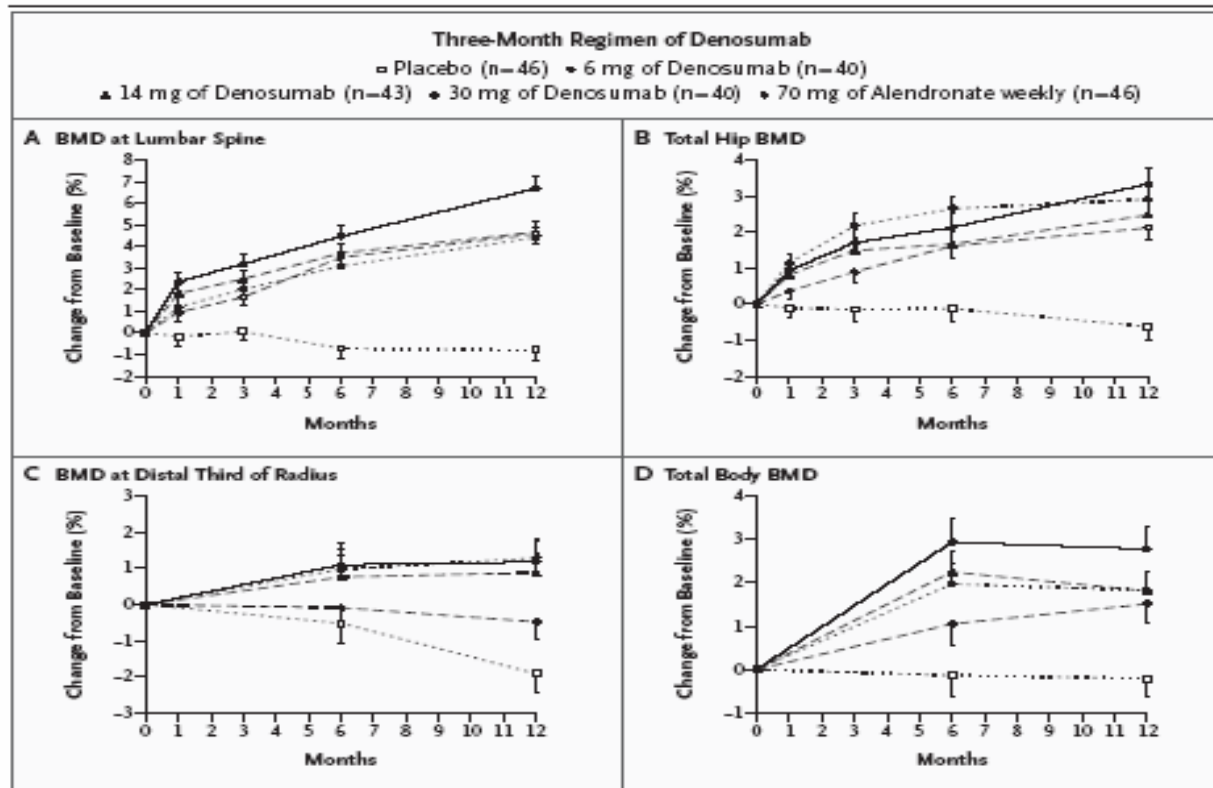
- The efficacy and safety of subcutaneously administered denosumab were evaluated over a period of 12 months in 412 postmenopausal women with low bone mineral
- Subjects were randomly assigned to receive denosumab either every three months (at a dose of 6, 14, or 30 mg) or every six months (at a dose of 14, 60, 100, or 210 mg), vs. open-label oral alendronate once weekly (at a dose of 70 mg), or placebo.
- The primary end point was the percentage change from baseline in bone mineral density at the lumbar spine at 12 months.
- Changes in bone turnover were assessed by measurement of serum and urine telopeptides and bone-specific alkaline phosphatase.

RANKL- Ab (Denosumab)

- Denosumab treatment for 12 months resulted in an increase in BMD at the lumbar spine of 3.0 to 6.7 % (as compared with an increase of 4.6 % with alendronate and a loss of 0.8 % with placebo),
- At the total hip an increase of 1.9 to 3.6 % (as compared with an increase of 2.1 % with alendronate and a loss of 0.6 % with placebo), and
- At the distal third of the radius an increase of 0.4 to 1.3% vs. decreases of 0.5 % with alendronate and 2.0% with placebo
- Near-maximal reductions in mean levels of serum C-telopeptide from baseline were evident three days after the administration of denosumab.
- The duration of the suppression of bone turnover appeared to be dose-dependent.

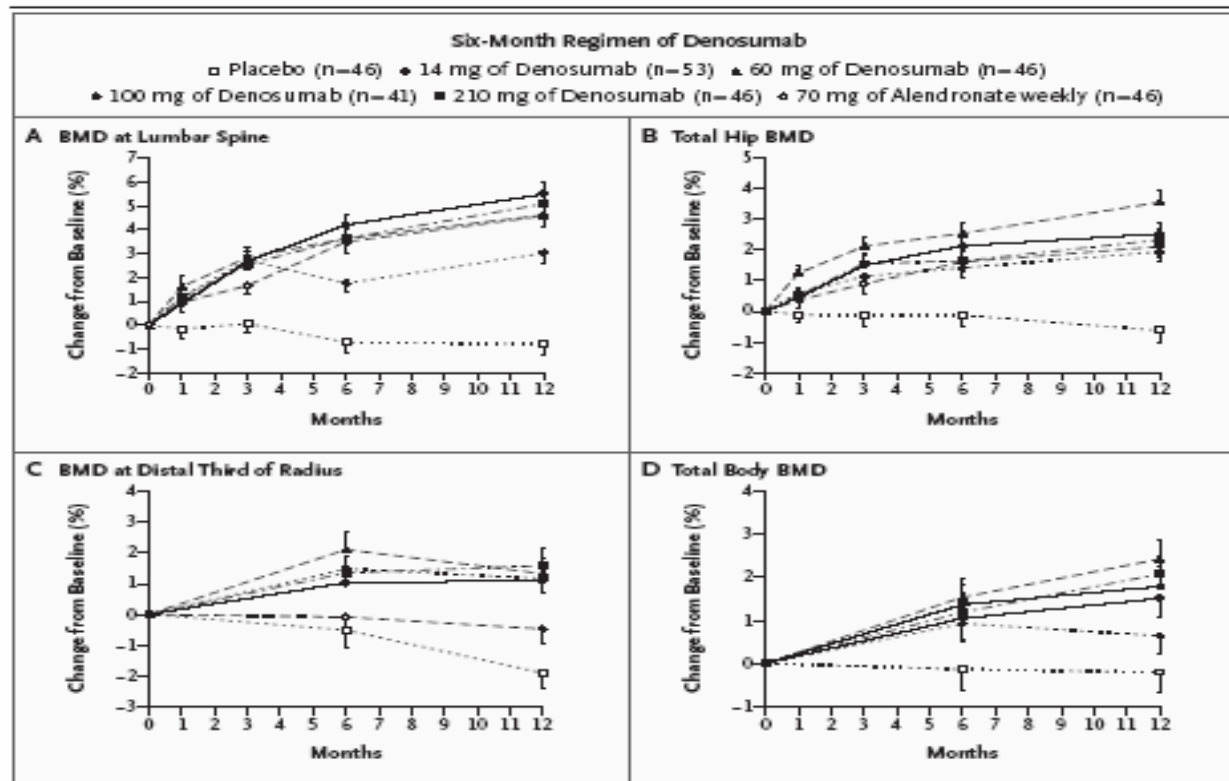
RANKL- Ab (Denosumab)

DENOSUMAB IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY



RANKL- Ab (Denosumab)

DENOSUMAB IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY



Receptor Activator of Nuclear Factor- κ B Ligand Antibody

- Despite treatment options that reduce the risk of fracture in patients with osteoporosis, few patients fully adhere to current therapies.
- A recent study reported one-year adherence rates of less than 25 % for all osteoporosis therapies examined.
- Thus, new treatment approaches that engender high adherence are needed.
- Receptor activator of nuclear factor- κ B ligand is one of these approaches being given SQ once every 3 or 6 months interval.

RANKL- Ab (Denosumab)

- In postmenopausal women with low bone mass, denosumab increased bone mineral density and decreased bone resorption.
- These preliminary data suggest that denosumab might be an effective treatment for osteoporosis.

Conclusions

- MS patients have an increased risk to develop osteoporosis
- Osteoporosis prevention, screening, and treatment protocols must be part of the medical plan for all MS patients
- Increased awareness and bone density screening of male and female MS patients over 40 years of age is warranted
- Understanding the causes associated with a decreased bone mass in MS patients, will help in defining the optimal gender appropriate therapeutic intervention.