International Journal of MS CARE
The Official Publication of the CMSC, RIMS and IOMSN

# Osteoporosis in Multiple Sclerosis: a Frequent, Serious, and Under-Recognized Problem

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## Abstract

*Osteoporosis and fractures are extremely common in the multiple sclerosis (MS) population, especially in those women with MS who are postmenopausal and not on hormone replacement therapy (HRT). There is evidence of significantly increased fracture risk in MS patients who have been on steroids, although this appears to be due to increased falls in addition to osteoporosis. Additionally, evidence has indicated that high-dose pulse methylprednisolone has little effect on osteoporosis, but decreased mobility is a very significant factor in decreased bone density. Osteoporosis in MS results in part from causes present in the general population, but is significantly aggravated by immobility and probably by other drugs used to treat MS and its complications, including drugs known to increase bone loss (eg, diphenylhydantoin). Fractures in MS are a particularly serious problem in that the resulting immobility causes deconditioning. A fracture—any fracture—is a much more serious problem in those with MS than in the general population. For example, use of narcotics for pain control in the MS patient with a fracture can convert constipation to obstipation or even bowel obstruction. Deconditioning resulting from injury-related immobility recovers much more slowly than in healthy individuals, and may never return to the preinjury level. Often a fracture converts an individual from being ambulatory to permanent wheelchair status. With preventive measures and moderately effective therapy available, it is important to identify those at risk and initiate appropriate treatment.*

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Osteoporosis is a common and frequently serious problem in the general population, causing an estimated 1.3 million fractures per year in the United States alone.[1] While there are few studies on the subject, osteoporosis appears to be even more common and more serious in those with multiple sclerosis (MS),[2] but is seriously under-recognized. It causes considerable morbidity and occasional mortality in those affected.

Both osteoporosis and falls contribute to fractures in the MS population.[2] Low bone mass in these patient predicts fracture risk.[3-6] In the MS population, falls are common and are a significant factor contributing to fractures.[2] In the authors' experience, a painful fracture, often a hip or vertebral fracture, converts an individual who is ambulatory with walking aids to a wheelchair-dependent state. Since the lack of coordination and weakness experienced by many of those with MS leads to falls, the risk of fractures in this population is quite high. Despite this, a Medline search for articles in the past decade with the key words *multiple sclerosis* and *fracture* yielded only two articles.[2,7]

The severity of this problem is emphasized by an examination of results from the first eleven patients in whom we obtained vertebral bone density measurements after we became aware of the problem (see Table 1). Seven of our eleven patients meet criteria for osteoporosis, and the remaining four have osteopenia. All but three are men (owing to population bias of the

Veterans Administration medical center); however, this emphasizes the importance of this problem in men as well as women.

***Table 1.*** *Results of Bone Density Assessments in a Sample of MS Patients.*

| Age | Gender | T-score | EDSS* | Fracture? | Other factors |
|---|---|---|---|---|---|
| 65 | M | –5.9 | 8.5 | no | |
| 55 | M | –5.1 | 8.5 | no | seizures, low testosterone |
| 69 | M | -4.6 | 7 | patella | |
| 64 | M | -4.6 | 7 | no | |
| 60 | M | –4.4 | 7 | no | |
| 60 | M | –3.1 | 7 | tibia | |
| 56 | F | –2.7 | 7 | ankle | postmenopausal, on HRT |
| 56 | F | –2.5 | 2.5 | no | postmenopausal, on HRT |
| 40 | F | –2.2 | 9 | no | premenopausal, African-American |
| 53 | M | –1.6 | 5 | no | on Dilantin (phenytoin) |
| 59 | M | –1.2 | 7 | no | |

*Kurtzke Extended Disability Status Scale rating (0 = normal; 7 = wheelchair self-transfer; 10 = dead from MS).

It has long been possible to carry out some measures, such as calcium and vitamin D supplementation and hormone replacement therapy (HRT), to reduce the risk of osteoporosis; but until quite recently, there was no effective treatment that would significantly reduce fracture risk in those with established osteoporosis. With the development of bisphosphonate drugs (eg, alendronate [Fosamax®] and etidronate [Didronel®]) and the advent of the selective estrogen receptor modifiers (SERMs), there are now therapies that have been shown not only to increase bone density but to significantly reduce the risk of fractures.[8-11] Alendronate can be used at a low dosage to prevent bone loss and at a higher dosage to increase bone density.

Most of those who deal with neurologic disease consider management of osteoporosis outside their area of expertise and interest. Nevertheless, it is essential that we, as health professionals, become aware of the effects of the medications we use to treat neurologic diseases (eg, steroids, immunosuppressive agents, and antiepileptic drugs) on bone mass. We need to see that osteoporosis is identified when present and, once identified, is properly treated. Additionally, we need to identify those at risk and take steps to prevent or minimize bone loss.

## Causes of Osteoporosis

Some of the most common causes of osteoporosis are listed in Table 2.[12,13] The rate in postmenopausal white women who are not on hormone replacement is extremely high, and that risk is significantly increased by the presence of decreased mobility. Causes that are particularly likely to contribute to osteoporosis in the MS population are listed in Table 3. In addition to those with known risk factors for osteoporosis, one should check for osteoporosis in any individual with fractures that are inexplicable or are the result of seemingly trivial trauma.

There are several methods of determining bone density. The two most common are dual-energy x-ray absorptiometry (DEXA) and quantitative computerized tomography (QCT). The

former is less expensive, more accurate, takes only 10 minutes, and exposes the individual to minimal radiation.[14,15] Both provide a value in terms of standard deviations (SD) or T-score relative to age matched controls. A T-score of –1 equals –1 SD; –2 equals –2 SD, and so on. A bone density T-score of –1 to –2.5 is defined by the World Health Organization (WHO) as osteopenia, and a T-score less than –2.5 is defined as osteoporosis.[14] Severe osteoporosis is defined as a value –2.5 SD or lower, with concomitant fragility fractures. We have seen values as low as –5.9 in a male wheelchair patient with MS.

The relative risk of fracture is 2.0 for each SD below normal; that is, the risk of fracture doubles for each SD below normal.[6,8] Anyone who is at risk should be evaluated and considered for preventive therapy, even if not yet osteoporotic. Those with osteoporosis require treatment to reduce fracture risk. While the risk of osteoporosis is significantly less in patients of races other than Caucasian, it should not be ignored.

***Table 2.*** *General Risk Factors for Osteoporosis*

| |
|---|
| **Common risk factors** |
| Hypogonadism (particularly in postmenopausal women not receiving hormone replacement) |
| Chronic or recurrent use of corticosteroids |
| Small bone structure |
| Body weight under ideal |
| Family history of osteoporosis |
| Caucasian race |
| Low dietary calcium intake |
| Immobility |
| Sedentary lifestyle |
| Cigarette smoking |
| Alcohol abuse ( > 5 oz/day) |
| Aging |
| **Metabolic Causes** |
| Vitamin D deficiency |
| Malabsorption syndromes |
| Hyperthyroidism |
| Hyperparathyroidism |
| Lactose deficiency |
| Uremia |
| Hypogonadism |
| Cushing's syndrome |
| Multiple myeloma |
| Paget's disease of bone |
| Malignancies causing weight loss |
| **Medications and Drugs** |
| Long-term anticonvulsant drugs (especially diphenylhydantoin) |
| Long-term heparin |
| Caffeine |
| Synthroid |

***Table 3.*** *Common Causes of Osteoporosis in MS*

| |
|---|
| **Immobility, especially decreased weight-bearing activity** |
| **Underweight** |
| **Hypogonadism** |
| **Postmenopausal women not receiving hormone replacement** |
| **Testosterone deficiency in males with MS** |
| **Repeated corticosteroid use** |



## Evaluation of Individuals With Osteoporosis

Although osteoporosis is common in the elderly (particularly those who are disabled), once a diagnosis is made, some basic evaluation is indicated to discover or rule out possible causes other than, or in addition to, the obvious ones. A general history and physical examination will usually be adequate to detect evidence of malignancy, hyperthyroidism, or Cushing's syndrome, although evidence for the latter is often ignored in individuals who have been on steroids in the recent past. Serum calcium and phosphorus should be checked at least twice, and a 24-hour urine calcium analysis should be done to rule out hyperparathyroidism. If there is a possibility of hyperparathyroidism, levels of parathyroid hormone should be measured using parathyroid hormone by radio immunoassay (iPTH) evaluation. A panel of hepatic function tests should be completed to rule out liver disease, and serum creatinine and blood urea nitrogen (BUN) levels should be measured to rule out renal disease. A check of 25-hydroxy vitamin D level will rule out vitamin D malabsorption or deficiency. Additionally, serum protein and urine protein electrophoresis should be considered to rule out multiple myeloma. If any of these tests are positive, appropriate further investigation and evaluation and treatment by an internist is warranted. In men with MS, a measurement of testosterone level is indicated, since they have an increased risk of hypogonadism.

## Management of Osteoporosis

Disease management in individuals with both MS and osteoporosis has two major aspects. The first is prevention of falls and resultant fractures, and the second is prevention of and/or treatment for the osteoporosis itself; both are important. Fractures cause major disease management problems in persons with MS, making fracture prevention as important an aspect as treatment, which takes a considerable time to have an effect.

### Complications of Fracture

Fractures have serious consequences in MS. Patients need to be educated about the risks for fracture as well as about measures to prevent falls. The restricted activity incident to a fracture regularly leads to deconditioning to a point where ambulation is no longer possible. If ambulation is possible, it may take weeks or months of therapy to regain lost physical capabilities. Expected mortality rate is 6.3% in the total population; after a hip fracture the expected mortality rate is 36.7%.[15] While mortality may not actually reach the expected rate of 36.7% in the MS population, it is certainly going to be significant.

Ileus (obstruction of the intestines) is one complication of fracture. Due to narcotic use to control pain, the bowels—normally sluggish in MS—become essentially paralyzed. Most physicians are unaware of the seriousness of this problem and the need for preventive

measures. Another complication resulting from decreased mobility is thrombophlebitis, with the associated risk of pulmonary embolism. This is particularly significant following fracture of one of the lower extremities. Additionally, individuals with a Kurztke EDSS rating of 6 or higher almost always have some respiratory compromise and may have some dysphagia when stressed. Those whose rating is EDSS 7 or higher almost always have a markedly decreased respiratory capacity[17]—often as little as 1 L—accompanied by a weak ineffective cough. Following a painful fracture, these individuals are at risk for aspiration pneumonia, which can be life threatening.

**Prevention of falls**

Many of those with MS have a tendency to fall, but do not worry much about the risk falls represent. Often, denial is a big part of this problem. Individuals with MS and their families need to be educated and made aware of these risks. They need to know if their bones are weak and to realize that a fracture is a much more serious problem in MS than in those who are healthy. Individual assessment of the situations in which falls occur and development of strategies for fall prevention are part of this education.

Physiatrists, physical therapists, and MS nurses can play an important role in the education process. Nurses are more likely to be aware of falls, because they spend a great deal of time with patients and assume the most responsibility for patient education and situational risk assessment. Physical therapists and physiatrists are in the best position to assess physical capacity, to recommend or prescribe appropriate balance-aid equipment, and to help with the educational process.

A host of devices are available to reduce the risk of falls; these include canes and crutches, walkers, grab bars, bath and shower seats, and bedside commodes and urinals. Evaluation of where and when falls occur, education in preventive measures, and provision of appropriate aids are important in avoiding fracture.

**Prevention and Treatment of Osteoporosis**

The relative efficacy and associated risks/adverse events for agents used to treat osteoporosis are listed in Table 4. Alendronate is the only drug proven to decrease the risk of extremity fractures, whereas both alendronate and raloxifene (Evista®) decrease the risk of vertebral fractures. [9-11,18] In addition, nasal salmon calcitonin has been shown to reduce the risk of fracture at the spine by approximately one third (Novartis Corp., data on file). HRT has long been known to reduce osteoporosis and fracture risk, but good data on this are hard to find.

Raloxifene is in the SERM category of drugs, and its only listed indication for use is the prevention of osteoporosis in postmenopausal women. It appears not to have been tested in premenopausal women, and there are little data on its use in men. Its mode of action is similar to HRT, and the two should not be used concurrently. Alendronate, on the other hand, can be used in addition to HRT and can also be used in premenopausal women. We prefer to use alendronate for its proven effect on both extremity and vertebral fractures and greater effect on bone density. Alendronate can be irritating to the esophagus, is poorly absorbed in the presence of food, and requires special precautions. It should be taken first thing in the morning with a full glass (8 oz) of water. Nothing else—neither food nor medicine—should be taken for 1 hour afterward. It is important for patients to remain upright during this period to minimize the risk of esophageal irritation, which is the most common complication. Patients should not lie down until they have eaten.

Measures to reduce or prevent osteoporosis in those with MS include education regarding adequate calcium and vitamin D intake, avoidance of smoking and excessive alcohol intake, and regular exercise, particularly weight-bearing exercise. Smoking cessation is particularly important. In menopausal and postmenopausal women, HRT is indicated. The concern that

estrogen might make MS worse has been expressed, but there is no good evidence that estrogen adversely affects the disease process. Patients who are on chronic steroid therapy, regardless of the reason, should be on a preventive regimen for osteoporosis.

Assuming that we have eliminated or have treated causes of osteoporosis other than steroid effects and immobility, treatment is based on calcium and vitamin D supplementation and use of one of the available therapeutic agents. We recommend a regimen of calcium carbonate (or another calcium compound) 500 mg to 650 mg bid, vitamin D 400 IU qid, and alendronate 5 mg to 10 mg a day. In postmenopausal women, HRT is also indicated. Raloxifene might be used in place of HRT in this circumstance, but there is no data available on combined usage of alendronate and raloxifene.

Studies have shown that treatment with alendronate can reduce the risk of vertebral compression fracture, hip fracture, and wrist fracture by about 50% in the first 2 years of treatment as compared to raloxifene, which reduces vertebral compression fractures but has no demonstrated effect on extremity fractures. Given the significance of fractures in the MS population, it behooves us to identify those with osteoporosis and initiate therapy.

***Table 4.***[9-13] *Fracture Risk Reduction With Agents Used for Osteoporosis Prevention and Treatment.*

| Treatment | Relative Fracture Risk With Use | | Risks and Side Effects |
|---|---|---|---|
| | Spine | Hip | |
| Hormone replacement | 0.4-0.6 | ~0.6 | Increased risk of thrombophlebitis, uterine bleeding, breast enlargement; slightly increased risk of uterine cancer |
| Raloxifene (Evista®) | 0.5 | NS | 3.1-fold risk of thrombophlebitis |
| Calcitonin (Miacalcin®, Calcimar®) | ~.65 | NS | Nausea; allergic hypersensitivity reactions |
| Alendronate (Fosamax®) | 0.47 | 0.49 | Esophageal irritation;† ulcers; flatulence |
| Etidronate (Didronel®) | NS | NS | Must be given in 14-day cycle repeated every 3 months; not approved for treatment of osteoporosis in US; does increase bone density |

NS = no statistically significant effect demonstrated.
†Must be administered on an empty stomach with a full glass of water, with no food or medicine for 1 hour post-dose. The patient must remain upright during this time.

## Summary

Osteoporosis is a common, serious, and treatable condition in persons with MS—particularly those with reduced mobility—and results in fractures in a significant proportion of this population. Since effective treatment is available, it is incumbent upon us as MS professionals

to identify those at risk for osteoporosis and those who already have this condition. Once identified, appropriate intervention to reduce the risk of fracture is imperative.

## References

1. Abbott TA 3d, Lawrence BJ, Wallach S. Osteoporosis: the need for comprehensive treatment guidelines. *Clin Ther*. 1996;18:127-1349.
2. Troiano RA, Jofkowitz A, Cook, SD, Bansil S, Zito G. Rate and types of fractures in corticosteroid-treated multiple sclerosis patients. *Neurology.* 1192;42:1389-1391.
3. Miller PD, McClung M. Prediction of Fracture Risk: Bone Density. *Am J Med Sci*. 1996;312:257-259.
4. Ross PD. Prediction of Fracture Risk II: Other Risk Factors. *Am J Med Sci*. 1996;312:260-269.
5. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med.* 1998;339:292-299.
6. Huisl SL, Siemende CW. Age and Bone Mass as a Predictor of Fracture in a prospective study. *J Clin Invest.* 1988;8:1804-1809.
7. Schwid SR, Goodman AD, Puzas JE, et al. Sporadic corticosteroid pulses and osteoporosis in multiple sclerosis. *Arch Neurol.* 1996;53:753-757.
8. Cummings SR, Black DM, Nevitt MC, et al. Appendicular Bone Density and Age Predict Hip Fracture in Women. *JAMA.* 1990;263:665-668.
9. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Arch Int Med.* 1997;157:2617-2624.
10. Lindsay R, Cosman F, Lobo RA, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab* 1999;84:3076-3081.
11. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Osteoporos Int. 1999;9:461-468
12. Finkelstein, JS. Osteoporosis. In: Bennett JC, Plum F, eds. *Cecil Textbook of Medicine.* Philadelphia, Pa: WB Saunders Company; 1996:1378-1384.
13. Krane, SM, Holick MF. Metabolic bone disease. In: Fauci AS, ed. *Textbook of Medicine.* New York, New York: McGraw-Hill; 1998.
14. Kanis JA. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9:1137-1141

15. Miller PD, Bonnick SL. Clinical application of Bone Densitometry. In: Favus MJ, ed. *Primer on Metabolic Bone Disease and Disorders of Mineral Metabolism*. Baltimore, Md: Lippincott Williams and Wilkins; 1997.
16. Lyons AR. Clinical outcomes and treatment of hip fractures. *Am J Med*. 1997;103(2A):51S-63S
17. Smeltzer SC, Utell M.J, Rudick RA, Herndon RM. Pulmonary function and dysfunction in multiple sclerosis. *Arch Neurol*. 1988;45:1245-1249.
18. Ettinger, B, Black, DM, Mitlak, BH et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA.* 1999;282:637-645.