Osteoporos Int (2010) 21:[Suppl2]S425–S429
DOI 10.1007/s00198-010-1251-0

REVIEW

Osteoporosis: disease severity and consequent fracture management

C. Cooper

Received: 19 February 2010 / Accepted: 22 March 2010
© International Osteoporosis Foundation and National Osteoporosis Foundation 2010

Abstract Osteoporosis is a systemic skeletal disease responsible for the high incidence of fractures in older subjects, particularly in postmenopausal women. The increasing prevalence with population ageing and prolonged life expectancy raises the rates of associated morbidity, loss of independence, and mortality. BMD and previous fracture history are two main risk factors associated with osteoporosis such that the presence of prior fractures can predict future fractures. Strontium ranelate is an agent developed for the management of postmenopausal osteoporosis, demonstrated to reduce vertebral, nonvertebral, major nonvertebral, and hip fractures. It has been demonstrated to be effective for a broad spectrum of patients, including women with osteopenia, osteoporosis, and severe disease.

Keywords Nonvertebral fracture · Osteopenia · Osteoporosis · Strontium ranelate · Vertebral fracture

Introduction

Osteoporosis is a systemic skeletal disease that has long remained underdiagnosed and poorly understood. In the past, lack of epidemiological data and insufficient methods of investigation together with the silent development of the disease has led to considerable under-recognition of osteoporosis in clinical practice [1]. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.

This systemic disorder constitutes a major public health concern since the induced increase in bone fragility and susceptibility to fracture negatively impact the quality of life of affected patients, and their direct and indirect effects on society are generally underestimated [1]. They impose a considerable economic burden on health care systems, and the disease may have severe and debilitating consequences at advanced stages or when left untreated, raising the rates of associated morbidity, loss of independence, and mortality [2–4].

Osteoporosis means, etymologically, porous bone and bone porosity is due to a reduction in bone mass associated with impaired bone architecture [1, 5]. In 1994, the World Health Organization (WHO) proposed a set of diagnosis criteria and a stratification of the disease based on the value of bone mineral density (BMD) and a history of fracture [6, 7]. However, this only takes into account the deterioration in mineralization and does not reflect the decline in microarchitecture. More recently, the development of fracture risk assessment tools, such as FRAX, incorporating risk factors such as age and severity of disease (e.g., level of BMD and the presence or absence of prevalent fractures) means that decisions regarding treatment can be made from a more informed position.

Prevalence of disease and fracture risk assessment

Osteoporosis is a widespread condition, which may have devastating health consequences through its association with fragility fractures. It is recognized clinically by

C. Cooper (✉)
MRC Epidemiology Resource Centre,
University of Southampton,
Southampton SO16 6YD, UK
e-mail: cc@mrc.soton.ac.uk

C. Cooper
Institute of Musculoskeletal Sciences,
University of Oxford,
Oxford OX3 7LD, UK

characteristic fractures that occur when abnormally fragile bone is subjected to relatively mild trauma. The most common fragility fracture sites appear to be the vertebral bodies of the thoracolumbar spine, the distal forearm, and the hip [4], and hip fractures are one of the most serious outcomes of the disease.

In 2004, it was estimated that 10 million Americans over the age of 50 had osteoporosis, with around 1.5 million fragility fractures each year, with another 34 million at risk of the disease [8]. A similar fracture occurrence has been observed in the UK, [9] suggesting that one in two women aged 50 years will have an osteoporotic fracture in their remaining lifetime, and the figure for men is one in five.

Osteoporosis is common among elderly people, and the prevalence of osteoporotic fractures increases with the aging population and increasing life expectancy [3, 9–11]. In both men and women after the age of 40, bone mass decreases from 0.5% to 1% each year. It has been observed, however, that osteoporotic fracture is twice more prevalent among older women as among men [3, 9]. With the age-related decline in bone mass, the risk of fracture increases, especially in women in whom bone is quickly lost with an average of 2% to 3% per year during the first 5 years after the menopause [12]. With the menopause, estrogen deficiency increases the rate of remodeling, and the balance of turnover between bone formation and bone resorption is in favor of resorption [12]. The Markov model that has been developed to estimate the risk of fragility fracture predicts that 35% of 50-year old women will sustain a vertebral deformity, 18% a hip fracture, and 17% a wrist fracture in their remaining lifetimes [13].

Fractures are not only associated with considerable morbidity, but also with a severe risk of death (±25%) within 1 year [13, 14]. Although the patterns of associated mortality differ between hip and vertebral fractures, both types of fracture are observed to be associated with impaired survival [9] and to be greater in subjects with coexisting illnesses and poor prefracture functional status [10]. The cause of reduced life expectancy is usually attributable to comorbid conditions rather than to the fracture itself [10].

Prospective studies have shown that there is a heightened risk of almost all types of fracture in individuals with low bone density irrespective of fracture site. Furthermore, prior fractures predict future fractures (Fig. 1). Women with a prior fracture have an 86% chance of developing a subsequent fracture. One in five postmenopausal women with prior vertebral fractures will experience another vertebral fracture within 1 year [14]. Despite these statistics, eight in ten women do not receive treatment during the year following an osteoporosis-related fracture [15].

Recently, the fracture risk assessment tool, FRAX™, was developed with the WHO [16, 17]. FRAX is an assessment algorithm that aims to predict the risk of hip and other osteoporotic fractures and includes independent clinical risk factors (age, gender, body mass index, prevalent fracture, and family history), alone or in combination with BMD values [16]. The use of FRAX in clinical practice provides valuable help in case finding for subjects at the highest risk of fracture and the prediction of fracture in osteoporotic subjects, and assists with the problem of underdiagnosis [16, 17]. For example, when using BMD, age, and previous fracture history, one can estimate the 10-year probability of hip and other fractures. Thus, a woman at age 60 years with an average BMD (about −1.4) has an average 10-year probability of hip fracture of around 2.4%. However, if she has previously had a fragility fracture, this risk increases to 4.8%.

BMD, therefore, remains one of the key parameters to be assessed in osteoporosis. The three stages of disease severity as defined by the WHO are graded according to BMD thresholds. The classification uses cut-offs based on standard deviation (SD) reductions in BMD from young adult normal means (1 SD) measured by standard densitometry: the first stage, osteopenia, induces a pathologic

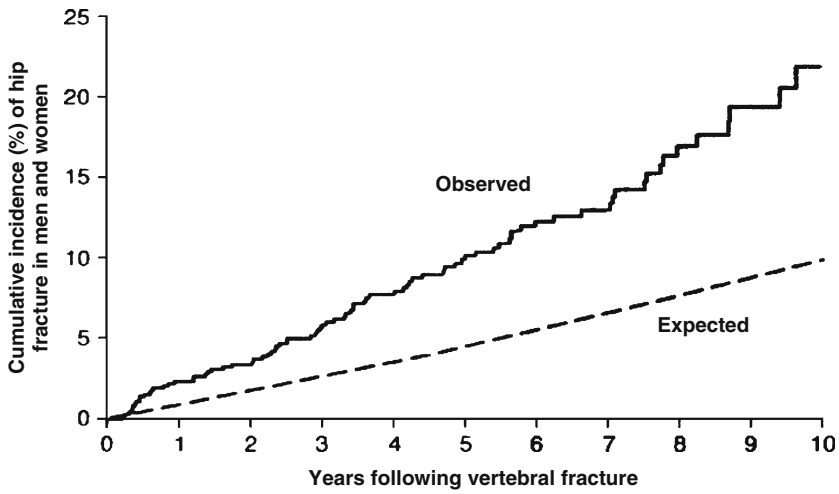

Fig. 1 Prevalent vertebral fracture predicts risk of future hip fracture. Adapted from Ref [14] with permission of John Wiley & Sons

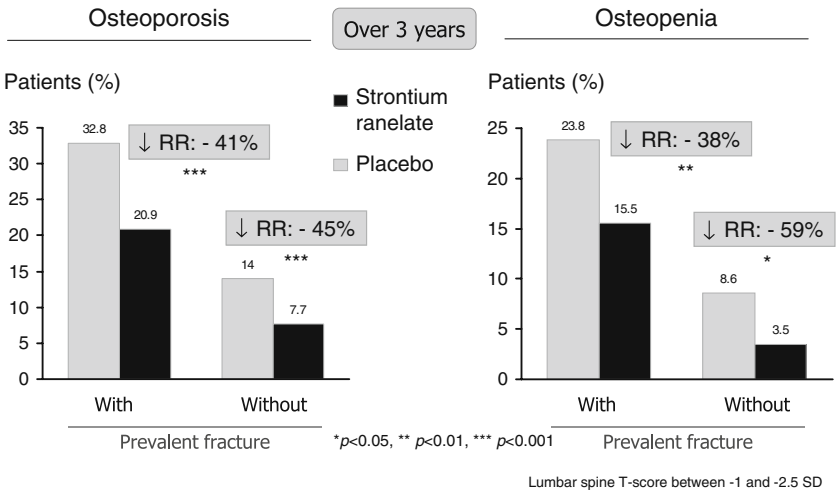

Fig. 2 Strontium ranelate decreases the risk of vertebral fractures whatever the severity of osteoporosis. Adapted from Ref [20] with permission of John Wiley & Sons

decrease of BMD (between 1 and 2.5 SD) with or without apparent symptoms; the second induces an alteration of bone mass (BMD decrease >2.5 SD) and a bone fragility with or without fractures; and the third stage or severe osteoporosis, also characterized by a reduction in BMD >2.5 SD below the mean but additionally the occurrence of one or more fractures.

However, as can be seen in the example mentioned above, it is particularly notable that the majority of fractures occur in osteopenic patients, i.e., in patients with a relatively slight decrease in BMD, which indicates that despite the fact that it provides important information about osteoporotic fracture risk, BMD is not the only factor contributing to fractures. This also highlights limitations of BMD measurements in monitoring the response to a therapy [18, 19]. In osteoporosis, microarchitecture is also a key determinant of bone quality, the impairment of which leads to decreased bone strength. The ability of a bone to resist fracture (or "whole bone strength") depends not only on the bone mass, but also on its spatial distribution (macro- and microarchitecture), and the intrinsic properties of the materials that constitute the bone. Quantitative assessment of macro- and microstructural bone features improve our ability to estimate bone strength. Thus, knowledge of bone microarchitecture is essential for understanding the pathophysiology of osteoporosis, determining the quality of bone, predicting fractures, and evaluating the efficacy of a treatment. The response of microarchitectural parameters to treatment should assess the real efficacy of anti-osteoporotic treatments, which are primarily expected to stop the progression of disease and prevent fractures.

How does strontium ranelate address the needs of patients of varying disease severity?

Two major randomized, double-blind, placebo-controlled, phase III studies have demonstrated the ability of strontium ranelate to reduce vertebral, nonvertebral, major nonverte-

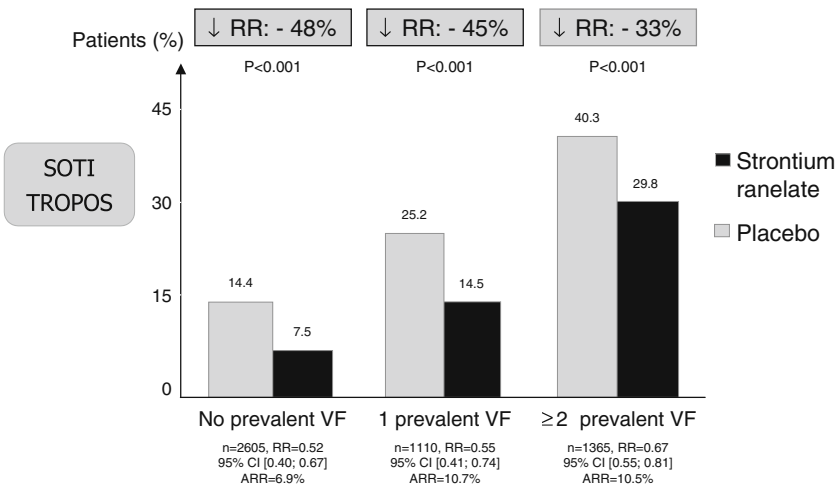

Fig. 3 Strontium ranelate decreases the risk of vertebral fractures over 3 years whatever the number of prevalent fractures. Adapted from Ref [23] with permission of John Wiley & Sons

bral, and hip fractures over 1, 3, 4, and 5 years [20–24]. Strontium ranelate has a unique mode of action, based on an uncoupling between increasing bone formation and decreasing bone resorption, resulting in bone turnover which is in favor of formation [25–29].

Strontium ranelate decreases the risk of vertebral fractures over 3 years both in women with lumbar spine osteopenia and any BMD value at the femoral neck and also in women with osteopenia at both sites [20]. A 41% reduction in the risk of vertebral fractures was demonstrated in women with lumbar spine osteopenia corresponding to a 59% reduction in those without prevalent fractures and 38% in those with prevalent fractures. In women with osteopenia at both sites, the risk was reduced by 52% (Fig. 2) [20].

In osteoporotic patients both with and without prevalent fractures, treatment with strontium ranelate resulted in early and sustained reductions in the risk of vertebral fractures [23]. The TROPOS study [22] demonstrated that strontium ranelate significantly reduced the relative risk of all nonvertebral fractures by 16% in the entire population, and by 19% for major fragility fractures. In a subgroup analysis of 1,977 osteoporotic women at higher risk of hip fracture (those ≥74 years and with femoral neck BMD T-score≤−2.4 SD), the risk of hip fractures was reduced by 36% over a 3-year period. In the subgroup without prevalent vertebral fractures, the relative risk was reduced by 45%.

Strontium ranelate was also observed to decrease the risk of vertebral fractures over 3 years even in patients with more than two prevalent fractures—a reduction in incident vertebral fracture risk by 40% was shown after 3 years and this effect was independent of age, initial BMD, and prevalent vertebral fractures. The risk of experiencing a first vertebral fracture was reduced by 48% ($p<0.001$), the risk of experiencing a second vertebral fracture was reduced by 45% ($p<0.001$), and that of experiencing more than two vertebral fractures was reduced by 33% ($p<0.001$; Fig. 3) [23].

A high correlation was identified between increasing BMD using strontium ranelate and the reduction in fracture risk in a study conducted to analyze the relationship between BMD changes and fracture incidence during 3-year treatment with strontium ranelate [23, 24]. This observation is supported by preclinical studies, which also demonstrate a robust correlation between the increase in BMD during strontium ranelate treatment and improvement in biochemical properties of the vertebral and upper femoral extremity [30]. This high correlation could be in part mediated by its action on markers of bone formation which is significantly increased after treatment with strontium ranelate [31]. An increase in femoral neck BMD after 3 years of treatment with strontium ranelate was statistically associated with a reduction of hip fracture incidence ($p=0.04$); at 3 years, for each 1% increase in femoral neck BMD, the risk of a hip fracture after 3 years decreased by 7% [24].

The strong correlation between measured BMD increases and fracture risk reduction in patients on strontium ranelate therapy should be of clinical benefit to physicians wishing to evaluate both treatment persistence and fracture risk reduction [32].

These relationships observed between strontium ranelate-induced changes in BMD and reduction in fracture risk are less clear with other types of anti-osteoporotic agents [33–36]. For example, in a study with raloxifene, despite the fact that raloxifene-treated patients had a statistically significant lower vertebral fracture risk compared with placebo-treated patients, this lowered risk appeared unrelated to treatment-induced change in BMD hence the authors concluded that the BMD changes obtained with raloxifene therapy were poor predictors of vertebral fracture risk reduction [33]. Similarly, Cummings et al. observed that improvement in spine BMD during treatment with anti-resorptive drugs accounted for a predictable but small part of the observed reduction in the risk of vertebral fracture [35].

Conclusion

BMD together with other fracture risk factors such as previous fracture history can be utilized to derive absolute risks of fracture and thresholds at which treatment for osteoporosis should be initiated. Strontium ranelate is a first choice treatment of postmenopausal women with osteoporosis with a broad spectrum of activity that covers women with osteopenia, osteoporosis, and severe osteoporosis. Irrespective of disease severity, this agent has proven its efficacy against osteoporotic fractures. Clinical benefits can be expected from this treatment for the affected patients and also societal benefits related to a better management of the disease.

Conflicts of interest C.C. performs consulting and lecturing with Servier, MSD, Lilly, Alliance, Amgen, and Novartis.

References

1. Siris S, Miller PD, Barrett-Connor E (2001) Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results from the National Osteoporosis Risk Assessment. JAMA 286:2815–2822
2. Consensus development conference (1993) Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 94(6):646–650
3. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd (1992) Incidence of clinically diagnosed vertebral fractures: a population-

based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res 7(2):221–227
4. Cooper (1997) The crippling consequences of fractures and their impact on quality of life. AM J Med 103(2):12S–19S
5. Manolagas SC (2000) Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 21:115–137
6. Kanis JA, and the WHO Study Group (1994) Assessment of fracture risk and its application to screening for post-menopausal osteoporosis: synopsis of a WHO report. Osteoporos Int 4:368–381
7. Kanis JA, Melton LJ III, Christiansen C et al (1994) The diagnosis of osteoporosis. J Bone Miner Res 9:1137–1141
8. US Department of Health and Human Services (2004) Bone health and osteoporosis: a report of the surgeon general. Rockville, MD
9. van StaaTP D, EM LHG, Cooper C (2001) Epidemiology of fractures in Wales and England. Bone 29:517–522
10. Cooper C, Harvey N, Dennison E (2008) Worldwide epidemiology of osteoporotic fractures. In innovation in skeletal medicine: 95–112. Rizzoli and Reginster ed
11. Cooper C, Atkinson EJ, Kotowicz M, O'Fallon WM, Melton LJ 3rd (1992) Secular trends in the incidence of postmenopausal vertebral fractures. Calcif Tissue Int 51(2):100–104
12. Dempster DW (2006) Anatomy and functions of the adult skeleton. In: Favus MJ, et al, eds. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 6th ed. Washington, DC: American Society for Bone and Mineral Research:7-11
13. Chrischilles EA, Butler CD, Davis CS, Wallace RB (1991) A model of lifetime osteoporosis impact. Arch Intern Med 151:2026–2032
14. Lindsay R, Silverman S, Cooper C et al (2001) Risk of new vertebral fracture in the year following a fracture. JAMA 285:320–323
15. Brown SA, Rosen CJ (2003) Osteoporosis. Med Clin North Am 87:1039–1063
16. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A, National Osteoporosis Guideline Group (2008) Case finding for the management of osteoporosis with FRAX—assessment and intervention thresholds for the UK. Osteoporos Int 19(10):1395–1408
17. available on www.shef.ac.uk/FRAX
18. Sandhu SK, Nguyen ND, Center JR, Pocock NA, Eisman JA, Nguyen TV (2010) Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. Osteoporos Int 21(5):863–871
19. Hosoi T, WHO FRAX(R) (2009) Usefulness and limitation of FRAX(R) in the practice of internal medicine. Clin Calcium 19 (12):1749–1755
20. Seeman E, Devogelaer JP, Lorenc R et al (2008) Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. J Bone Miner Res 23(3):433–438
21. Meunier PJ, Roux C, Seeman E et al (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Eng J Med 350(5):459–468
22. Reginster JY, Seeman E, de Vernejoul MC et al (2005) Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90:2816–2822
23. Roux C, Reginster JY, Fechtenbaum J et al (2006) Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. J Bone Miner Res 21(4):536–542
24. Bruyère O, Roux C, Badurski J et al (2007) Relationship between change in femoral neck bone mineral density and hip fracture incidence during treatment with strontium ranelate. Curr Med Res Opin 23(12):3041–3045
25. Reginster JY, Sarlet N, Lejeune E, Leonori L (2005) Strontium ranelate: a new treatment for postmenopausal osteoporosis with a dual mode of action. Curr Osteoporos Rep 3(1):30–34
26. Marie PJ (2005) Strontium ranelate: a novel mode of action optimizing bone formation and resorption. Osteoporos Int Suppl 1:S7–S10
27. Marie PJ (2006) Strontium ranelate: a dual mode of action rebalancing bone turnover in favour of bone formation. Curr Opin Rheumatol Suppl 1:S11–S15
28. Brennan TC, Rybchyn MS, Green W et al (2009) Osteoblasts play key roles in the mechanisms of action of strontium ranelate. Br J Pharmacol 157(7):1291–1300
29. Neuprez A, Hiligsmann M, Scholtissen S, Bruyere O, Reginster JY (2008) Strontium ranelate: the first agent of a new therapeutic class in osteoporosis. Adv Ther 25(12):1235–1256
30. Ammann P, Shen V, Robin B et al (2004) Strontium ranelate improves bone resistance by increasing bone mass and improving architecture in intact female rats. J Bone Miner Res 19:2012–2020
31. Recker R, Marin F, Ish-Shalom S et al (2009) Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis. J Bone Miner Res 24(8):1358–1368
32. Kendler DL, Adachi JD, Josse RG, Slosman DO (2009) Monitoring strontium ranelate therapy in patients with osteoporosis. Osteoporos Int 20(7):1101–1106
33. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res 17(1):1–10
34. Watts NB, Geusens P, Barton IP, Felsenberg D (2005) Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. J Bone Miner Res 20:2097–2104
35. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment antiresorptive drugs. Am J Med 112(4):281–289
36. Delmas P, Seeman E (2004) Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 34:599–604