CHAPTER 77

Osteoporosis: burden, diagnosis, and management

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Introduction

The World Health Organization (WHO) defines healthy ageing as the process of developing and maintaining the functional ability that enables well-being in older age.[1] Maintenance of musculoskeletal health during ageing is a key determinant of functional ability. Osteoporosis (OP) is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[2] OP is a major contributor to the global burden of disease and disability worldwide. Prevention and management of this disorder are of increasing importance, with pressure mounting from the ageing population.[3,4]

Global epidemiology of fragility fractures and regional disparities

As the world population has aged over the last three decades, the incidence of hip fracture has increased significantly. In 1990, it was estimated that 1.3 million hip fractures occurred worldwide, and the prevalence of hip fracture sufferers living with disability was almost 4.5 million.[5] By 2010, the global incidence of hip fracture was estimated to have increased to 2.7 million cases per year.[6] The most recent estimate of the prevalence of any fragility fracture, defined as the number of individuals suffering disability, was 56 million worldwide in the year 2000.[7] In 2015, Kanis and colleagues sought to quantify the number of individuals worldwide age 50 or more at high risk of fracture in 2010 and 2040.[8] High fracture probability was defined as the age-specific 10-year probability of suffering a major osteoporotic fracture (i.e. hip humeral, wrist, or clinically apparent vertebral fracture), which was equivalent to that of a woman with a body mass index (BMI) of 24 kg/m² and a prior fragility fracture but no other clinical risk factors for fracture. In 2010, 21 million men (3.1%) and 137 million women (18.2%) had a fracture probability at or above the threshold. The number of men and women combined who will be above the threshold is expected to almost double from 158 million in 2010 to 319 million in 2040.

Marked variations in the incidence of hip fractures, the prevalence of vertebral fractures, and the 10-year probability of major osteoporotic fractures have been reported for different regions of the world. Age-standardized rates vary approximately 10-fold for both men and women according to the considered region of the world. Why hip fracture risk varies so much between countries is not currently known. Environmental factors may play a greater role than genetic factors. Epidemiological studies of immigrant populations lend support to this hypothesis. While African-Americans leaving in the United States have lower fracture probabilities than their Caucasian countrymen and women, their hip fracture risk is higher than native Africans.[9] Similar patterns are observed for the Japanese populations of Hawaii[10] and Chinese living in Hong-Kong or Singapore.[11] During the next three decades, the demographic shift in Asia, Africa, and Latin America will result in these regions bearing the brunt of the increasing hip fracture incidence worldwide. In 2017, the prevalence and incidence of vertebral fractures worldwide[12] suggested that the highest rates were reported for Scandinavia (26%); intermediate rates for Western Europe, the US, and Mexico (20%); and low rates for Latin America (15%). Studies concerned with the incidence of vertebral fractures were comparatively sparse. Studies that combined individuals with vertebral fractures who were either hospitalised or ambulatory indicated that the highest age-standardised rates were evident in South Korea, the US, and Hong Kong, while the lowest rate was in the UK.

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More than 3.5 million osteoporotic fractures occur annually in Europe.[13,14] A review of the clinical and economic burden of osteoporotic fractures in 27 European countries in 2010 found that two-thirds of all incident fractures occurred in women, and fracture incidence increased with age with the majority of hip fractures reported in patients ≥80.[13] The most common fractures were hip (18%), forearm (16%), vertebrae (15%), and 'others' (51%).[13] Other studies have also highlighted the importance of non-hip and non-vertebral (NHNV) fractures, with up to 70% of fractures occurred in NHNV locations in postmenopausal women receiving bone-loss therapies in a primary care setting.[15]

Geographically, fracture incidence varies widely by country across Europe.[11,15] Compared with other regions of the world, Europe has some of the highest hip fracture rates, with an apparent north-south gradient, and most countries are categorised as high or moderate risk.[11] However, this variation between countries is not as pronounced for vertebral fracture incidence,[16] at least when judged by vertebral morphometry. Socioeconomic factors have been hypothesised as the most likely explanation for the heterogeneity of fracture incidence between communities, but other factors are also candidates, such as sunlight exposure, low calcium intake, physical activity, low BMI, anthropometric variables, and race.[13,17]

Substantial temporal trends in age-specific rates of hip fractures have been observed in recent decades. With a few exceptions, age-specific incidence rates rose in Western populations until around 1980 and have since reached a plateau or declined.[16] In the case of hip fracture incidence rates, an earlier reversal of this trend and a higher peak fracture incidence have been demonstrated in Northern European countries compared with the later trend for reversal and lower peak fracture incidence in some Southern European countries.[18] A recent study of the hip fracture trend in Sweden and Denmark found that period and cohort effects, which may reflect environmental and lifestyle factors, contributed to this observation, and analyses indicated that age-specific hip fracture rates were likely to increase again in the near future.[14,18] Further to this, the number of people with OP in Europe has been predicted to rise by 23% from 27.5 million in 2010 to 33.9 million in 2025, due to the increasing proportion of elderly people. Consequently, the osteoporotic fracture rate is also expected to increase throughout Europe, with an increase of 56 and 41% predicted in the male and female population, respectively.[13,14]

Burden of osteoporosis

Hip and vertebral fractures are associated with increased mortality, with the mortality risk highest immediately after the fracture event and then decreasing with time.[19] In Europe, the number of deaths in 2010 directly related to fractures was estimated at approximately 20,100 in men and 22,700 in women, of which 49 and 33% were attributed to hip and vertebral fracture events, respectively.[13] The management of OP is also associated with a very high economic burden in Europe, with a high degree of variation between countries. In 2010, the cost of managing OP was estimated at 37 billion Euros. Despite this, there is currently minimal investment in pharmacological prevention, which makes up 5% of this cost, compared with the cost of treating incident fractures (66%) and long-term fracture care (29%).[13] As a proportion of the total spend, excluding expenditure for pharmacological prevention, hip fracture represents 54%, while 'other fractures' represented 39% and clinical vertebral and forearm fractures represented only 5 and 2%, respectively.[13] The significant impact of NHNV fractures, in particular on healthcare resources, has been demonstrated in several studies showing that NHNV resulted in a substantially higher number of days in the hospital and rehabilitation/nursing home care over a one-year period compared with vertebral and hip fractures.[20]

When considering quality-adjusted life-years (QALYs), which give a societal perspective on the burden of disease, the total health burden of OP in Europe was estimated at 1,165,000 QALYs, and twice as many QALYs were lost in women compared to men.[13] Hip fractures, clinical vertebral, forearm, and 'other' fractures incurred approximately 600,000 (52%), 344,000 (30%), 19,000 (2%), and 202,000 (17%) QALYs lost, respectively. For hip and vertebral fractures, approximately 79 and 59% of the QALYs lost were a consequence of prior fractures.[13] When the cause of OP was combined with the value for QALYs lost, the overall cost of OP amounted to 98 billion Euros in Europe in 2010.

The burden associated with OP has been shown to be higher than for other common non-communicable diseases. Total disability-adjusted life-years (DALYs) lost to OP in Europe, reflecting the years of life lost due to a fracture and the disability in those who survived, were 5.8 million in 2010, representing 0.83% of the global burden of non-communicable diseases. This loss in DALYs for OP was greater than for other diseases such as hypertensive heart disease and rheumatoid arthritis.[13] Furthermore, fracture due to OP accounted for more deaths and morbidity than any cancer type other than lung cancer.[13]

The already high healthcare costs of OP in Europe are predicted to increase in the future due to the growing elderly population.[14] The annual number of QALYs lost annually in Europe is expected to rise such that by 2025, it will have increased by 20% from 2010; the highest growth (32%) is forecast for the population age ≥80, who incur the highest costs for fractures compared with other age groups.[13] Overall, the total cost (including values of QALYs lost) in Europe is predicted to rise by 23%, from 98 billion Euros in 2010 to 120 billion Euros in 2025.

The osteoporosis treatment gap

There are now data from Europe and the US demonstrating substantial disparities between the number of individuals at high fracture risk or who have experienced a low-trauma fracture and the number who receive appropriate assessment and treatment for OP.[21] The probability of being prescribed any anti-osteoporosis drug after hip fracture in the UK increased from only 7% in 2000 to 46% in 2010.[22] This trend was more marked in patients age ≥75. The increase in prescriptions of anti-osteoporosis drugs was complemented by a similar increase in vitamin D/calcium provision. The cumulative incidence of anti-osteoporosis therapy was greater at any given point in time in women than in men. Despite <50% of hip fracture patients receiving treatment, more recent data suggest a plateau and a possible decrease in prescriptions from around 2011.[23] Additionally, data from a prospective observational study of over 60,000 older women recruited from primary care practices in 10 countries across the US, Europe, and Australia showed that >80% of women with a fragility fracture did not receive OP treatment.[24] In Europe, treatment uptake for OP increased progressively up to 2008, thereafter plateaued, and has subsequently fallen in more recent years. The phenomenon is most marked in the case of the bisphosphonates and is evident on a country-by-country basis.[25]

There is a very wide inter-country variation in the treatment penetration in individuals at high risk for OP fracture. The treatment gap varies from 25% in Spain to 95% in Bulgaria. Larger treatment gaps were identified in countries with populations at both high and low risk of fracture. In total, in the EU, it was estimated that out of the 21.3 million men and women who exceeded an intervention threshold set based on the FRAX-based 10-year fracture probability, 12.3 million were untreated in 2010.[26] In an international prospective study, low uptake of pharmacological intervention after hip fracture was also observed. Among 1795 patients who sustained a low-energy hip fracture in 10 countries (Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, and the UK), only 27% were prescribed pharmacological fracture prevention after the hip fracture.[25] There appear to be many factors in the treatment gap for OP, including insufficient implementation of strategies to affect primary and secondary prevention. It is apparent that musculoskeletal diseases may be viewed by both patients and policymakers as a lower priority than outcomes such as myocardial infarction and cancer.[21]

Approaches to closing this gap include identifying patients at high risk of fracture, primary fracture prevention, and secondary fracture prevention. Following attendance to a healthcare practitioner with a new fracture, it is important to assess fracture risk in a straightforward way and treat if appropriate. The most successful method usually focus on a multi-disciplinary fracture liaison service[27] incorporating orthogeriatricians, rheumatologists, other physicians and clinical nurse specialists. They work in a multi-disciplinary team to ensure that medical management of patients admitted for fracture is optimised, both in the hospital and for future fracture prevention, ideally with a lead clinician responsible for coordinating the team.[28] The International Osteoporosis Foundation (IOF) has recently instituted 'a global campaign to facilitate the implementation of coordinated multi-disciplinary models of care for secondary fracture prevention'.

Intervention and assessment thresholds[29,30]

The IOF and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommend expressing the risk of fracture as an absolute risk, i.e. probability of fracture over 10 years.[2,29] The absolute risk of fracture depends upon age and life expectancy as well as the current fracture risk. The period of 10 years was chosen to cover the likely length of treatment and the time over which benefits may continue or risks arise if treatment is stopped.[2] An algorithm that integrates the weight of clinical risk factors for fracture risk, with or without information on bone mineral density (BMD), was developed in 2007 by the then WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield. The resulting FRAX tool computes the 10-year probability of hip fracture or a major osteoporotic fracture (a clinical spine, hip, forearm, or humerus fracture). The tool has been extensively validated in independent cohorts[31] and calibrated to the epidemiology of fracture and death in 67 countries, covering more than 80% of the population at risk.[32]

FRAX has been incorporated into more than 100 guidelines worldwide, but the approach to intervention thresholds has varied widely.[32,33] In the European guidance,[2,29] it is recommended that postmenopausal women with a prior fragility fracture should be treated without further assessment, although BMD measurement and incorporation into the FRAX calculation is sometimes appropriate, particularly in younger postmenopausal women. In women without a previous fragility fracture, the management strategy should be based on an assessment of the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or humerus). Women with probabilities below the lower assessment threshold can be considered at low risk. Women with probabilities above the upper assessment threshold can be considered for treatment. Women with probabilities between the upper and lower assessment thresholds should be referred for BMD measurements and their fracture probability reassessed.[2] The age-dependent

intervention threshold is set at a risk equivalent to that associated with a prior fracture in a woman of the same age with average BMI and therefore rises with age.[34] The same thresholds are used in men since the cost-effectiveness of interventions is broadly similar in men and women.[35]

Some agencies have been reluctant to reimburse treatments based on fracture probability, particularly at younger ages where the 10-year probability of a major osteoporotic fracture is less than 10%. In the UK, for example, the intervention threshold for women age 50–54 is 8.18%. At the same age, however, the remaining lifetime probability of a major fracture is high (57%). Moreover, cost-effective scenarios for treatment are available at these levels of risk.[1,29]

In addition to the 10-year probability of a major osteoporotic fracture, the European guidance (Figure 77.1) also provides intervention thresholds based on the 10-year probability of hip fracture.[2,29] Either or both thresholds can be used: indeed, the screening for prevention of fractures in older women trial showed that a screening strategy decreased the incidence of hip fracture based on treatment targeted by hip fracture probability.[36] This assessment strategy permits the classification of risk. In addition to the categories of low and high risks, which were previously presented in the IOF-ESCEO guidelines,[2] very high-risk patients can be identified. *Very high risk* is defined as a fracture probability that lies above the upper assessment threshold after a FRAX assessment, with or without the inclusion of BMD: i.e. where BMD testing is unavailable, the same probability can be used[29] (Figure 77.2).

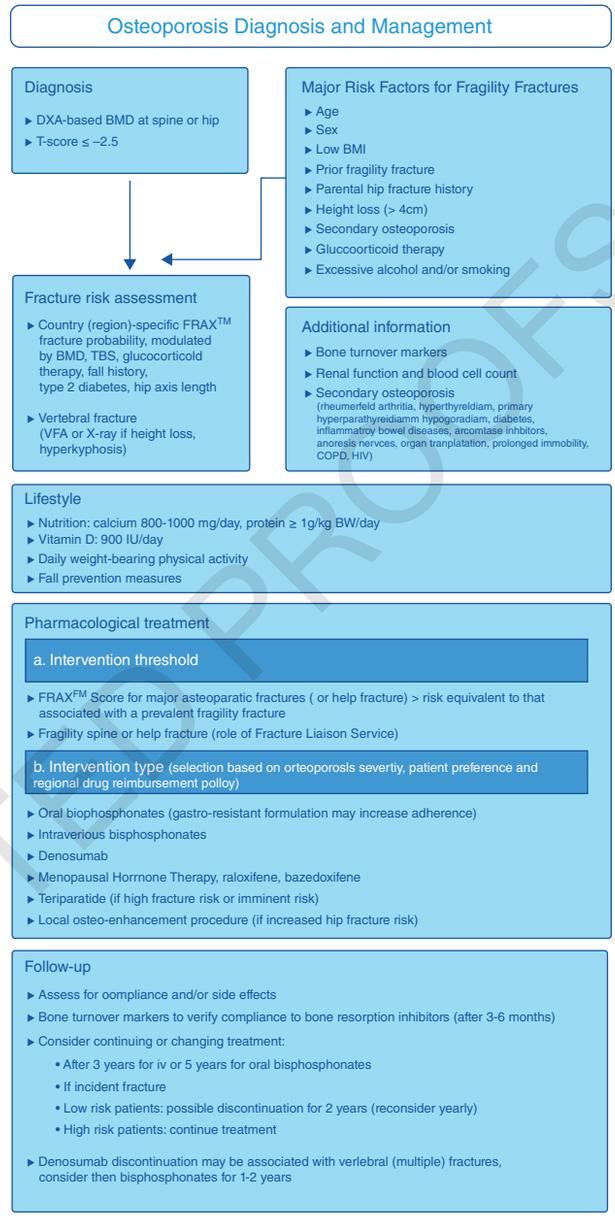

Figure 77.1 Algorithm for the diagnosis and management of osteoporosis in postmenopausal women. Source: Modified from Kanis et al.[30]

Management

Non-pharmacological management should be considered for all patients but may be adapted according to the category of fracture risk.[37] For all patients, education on OP (e.g. knowledge of OP, medications, diet, and exercise) and advice for daily weight-bearing physical activity are appropriate.[38-40] Where indicated, the addition of fall-prevention measures, including supervised exercise and/or rehabilitation, has been shown to be useful in reducing falls.[40] But the effect on fracture risk remains uncertain. The programme should continue for at least 50 hours, be progressive, and include strength and balance training components.[41]

All women should also receive appropriate calcium and vitamin D supplementation if needed.[29] If a woman is categorised as low risk, menopausal hormonal treatment and selective oestrogen receptor modulators CAN be considered.[29] In the treatment recommendations, women at high risk usually start with an inhibitor of bone resorption (including oral bisphosphonates or denosumab). In contrast, women at very high risk might be more suitably treated with an anabolic treatment (teriparatide and its biosimilars, abaloparatide, romosozumab), followed by an inhibitor of bone resorption.[2,29] If a very high risk of hip fracture is observed, particularly if following a first hip fracture, local osteo-enhancement procedure could be considered.[29] For oral bisphosphonates, formulations that improve adherence to treatment (e.g. gastro-resistant risedronate) should be privileged.[30,42,43]

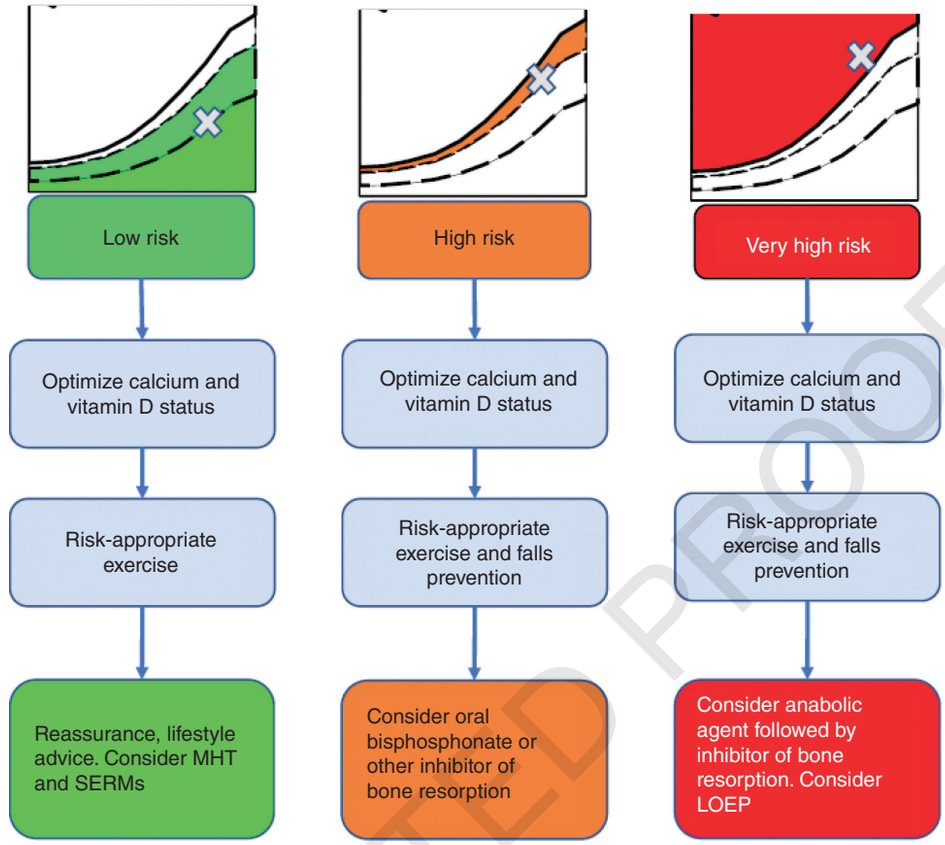

Figure 77.2 Treatment pathways according to the categorisation of fracture risk. Source: Kanis et al.,[29] © 2019 Springer Nature.

As previously mentioned, fracture liaison services provide a system for the routine assessment and management of postmenopausal women and all men who have sustained a fragility fracture. The benefits of a coordinator-based system to ensure appropriate management of patients following a fracture are well established. 'Capture-the-fracture', (CTF), launched by the IOF, promotes this approach to prevent a second fracture. This initiative aims to set internationally endorsed standards for best practice by facilitating the implementation of fracture liaison services involving best practice frameworks, multi-disciplinary models, and Fracture Liaison Services (FLS) questionnaires.

Conclusion

Osteoporosis generates a major clinical, social, ethical, and financial burden on patients and society. Despite a clear demonstration that patients at increased risk of OP benefit from appropriate management, the gap in the treatment of OP remains high in all parts of the world, particularly in elderly patients. The risk categorisation of individuals deemed to merit treatment into high and very high risk and the targeting of anabolic therapy followed by anti-resorptive medications to patients at imminent risk of presenting any new fracture, together with the implementation of fracture liaison services, are new approaches that are changing the paradigm of OP management, which hopefully will help to close the gap in the treatment of OP.

Conflict of interest

Jean-Yves Reginster has received advisory board or consulting fees from IBSA-Genevrier, Pierre Fabre, Radius Health, TEVA, and Mylan; lecture fees from AgNovos, IBSA-Genevrier, Mylan, CNIEL, Dairy Research Council (DRC), and Theramex; and institutional grants support from IBSA-Genevrier, Mylan, CNIEL, and Radius Health. Olivier Bruyere has no conflict of interest related to this chapter. Neither author received any financial or non-financial compensation for preparing this chapter.

Key points

- Maintenance of musculoskeletal health during ageing is a key determinant of functional ability.
- Osteoporosis is a major contributor to the global burden of disease and disability.
- The most common fractures are hip, forearm, and vertebrae.
- The already high healthcare costs of OP in Europe are predicted to increase in the future due to the growing elderly population.
- An algorithm (FRAX) that integrates the weight of clinical risk factors for fracture risk, with or without information on bone mineral density (BMD), computes the 10-year probability of hip fracture or a major osteoporotic fracture.
- Non-pharmacological management should be considered for all patients but may be adapted according to the category of fracture risk.
- All women should receive appropriate calcium and vitamin D supplementation if needed. Women at high risk usually start with an inhibitor of bone resorption (including oral bisphosphonates or denosumab). In contrast, women at very high risk might be more suitably treated with an anabolic treatment (teriparatide and its biosimilars, abaloparatide, romosozumab), followed by an inhibitor of bone resorption.
- Fracture liaison services provide a system for the routine assessment and management of postmenopausal women and all men who have sustained a fragility fracture.

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