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HANDBOOK

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Spotlight on osteoporosis

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Foreword

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fracture.

Osteoporosis frequently affects people over the age of 50 years – men as well as women, although it is more prevalent among women. In the European Union, based on data from 2010, approximately 22 million women and 5.5 million men between the ages of 50 and 84 years have osteoporosis. The number of men and women with osteoporosis is projected to rise by 23% to 33.9 million by 2025.

Working with a distinguished faculty of clinicians and thought leaders at the forefront of the field, the latest educational handbook from *Hospital Pharmacy Europe* aims to provide a comprehensive disease overview and up-to-date review of its risk factors and prevention, developments in screening and diagnosis, and management strategies.

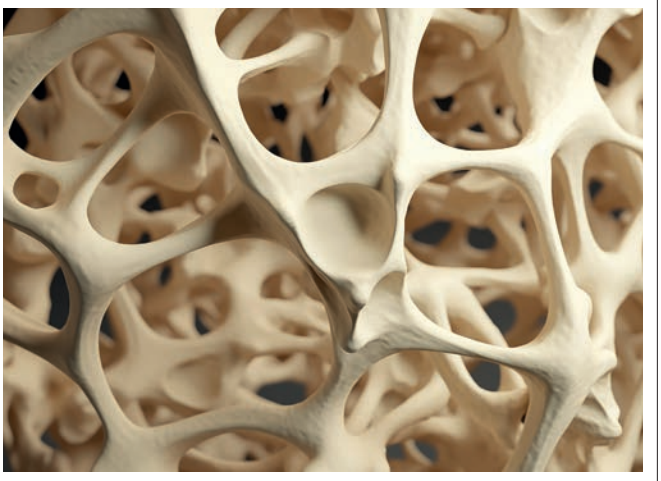
Bone is a dynamic tissue continuously removed and replaced; in other words, remodelled. To open the handbook, Professor Serge Ferrari discusses the pathophysiology of bone modelling and remodelling and how deficits in osteoporosis lead to bone instability and fragility. Understanding the processes that ensure the skeleton can perform its weight-bearing function, repair minor damage that results from mechanical stress and contribute to calcium homeostasis is vital in the quest for new treatments and developing prevention strategies for the disease.

As the population ages, the disease becomes more common and the burden of osteoporosis, especially as a result of osteoporotic fractures is significant. In his article, Professor Giovanni Adami considers its impact on the quality of lives of those affected, healthcare resources, the cost of social care, and the wider society.

The risk of developing the disease is governed by a number of factors, including age, gender and ethnicity as well as modifiable factors such as bone mineral density, diet, and levels of exercise and physical activity.

Modifying risk factors such as nutrition and lifestyle are crucial in preventing and managing osteoporosis. People at high risk may need pharmacological interventions to prevent fractures and Professor Roland Chapurlat educates on how to assess risk factors and tailor treatment to individual patients' circumstances.

Professor John Carey and Dr Attracta Brennan provide a comprehensive overview of screening and diagnosis and how techniques have evolved to help diagnose and grade the severity of osteoporosis. Fracture risk assessment tools are also considered. The correct use of the right algorithm and application of diagnostic and at-risk criteria to reduce the harms and waste associated with over-testing and over-treatment and to maximise value and the quality of care for those most likely to benefit is emphasised.



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The efficacy and tolerability of osteoporosis treatments and information about patient and drug selection is outlined by Professor Maria-Luisa Brandi. Some of the challenges of long-term management of osteoporosis are also discussed, and non-drug approaches are also summarised.

Osteoporosis treatments fall into three broad classes: anti-resorptive (inhibiting the osteoclasts); bone-forming (stimulating the osteoblasts); and dual-acting (simultaneously stimulating the osteoblasts and inhibiting the osteoclasts). They reduce the risk of fracture compared with placebo and may increase bone mineral density. A range of factors should be considered when deciding which therapeutic approach to take for each patient, including fracture risk assessment, patient suitability and preference, the latest clinical evidence and cost-effectiveness.

As treatment for osteoporosis is usually needed for long periods and current pharmacotherapy is limited by efficacy and tolerability data, sequential treatment is advocated. The optimal sequence of treatments has not yet been determined neither have the patients who would benefit most from such an approach. However, current knowledge about the disease and available therapies provides some pointers for clinicians as to the path that may be most logical.

We hope you find this handbook interesting, informative, and a valuable resource to supplement your knowledge and clinical practice regarding this burdensome, common condition.

Thank you for reading!

Pathophysiology of bone fragility

Bone should not only be considered a structural component of the human body but also a responsive, multifunctional tissue whose dysregulation can have significant implications, particularly in conditions such as osteoporosis, where remodelling balance is disrupted

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Bones are not merely structural components; they are dynamic organs that perform multiple, interdependent roles vital to physiological stability and function.[1,2] Beyond providing a rigid framework, bones safeguard internal organs, support movement by anchoring muscles, and serve as reservoirs for critical minerals such as calcium and phosphate. Within their trabecular spaces, bones house haematopoietic marrow, which is responsible for blood cell formation. Additionally, bones function as endocrine organs, secreting regulatory factors that influence phosphate metabolism, glucose homeostasis and more.[1,2]

Bone structure

The structural organisation of bone tissue is intricate, optimised for both strength and flexibility. Compact (cortical) bone – the hard outer layer – with its densely packed osteons, exemplifies this organisation. Each osteon features concentric lamellae surrounding a central canal, which houses blood vessels and nerves essential for nutrient delivery and waste removal. Spongy (cancellous) bone – the leaner interior layer – located at the metaphyses and epiphyses (ends) of long bones and within vertebral bones, provides structural support and extended bone surfaces for remodelling (see below) with a network of trabeculae, conferring strength without excessive weight.[1,2]

Bone cells and biology

Bone tissue undergoes continuous renewal and remodelling and its integrity and adaptability are maintained through the coordinated actions of four primary cell types: osteoclasts, osteoblasts, osteocytes, and lining cells. Each type performs a specialised role in balancing bone formation, resorption and structural adaptation, thereby maintaining bone integrity and metabolic function.

Osteoblasts

Osteoblasts are mononuclear cells derived from mesenchymal stem cells and are responsible for bone formation. By synthesising and depositing organic matrix components, primarily collagen, osteoblasts establish the scaffold upon which mineralisation occurs. This calcification process results in the hardening of bone tissue. Upon completing bone formation, osteoblasts can undergo apoptosis, and become embedded within the matrix as osteocytes.[1]

Osteoclasts

Osteoclasts, large multinucleated cells originating from hematopoietic stem cells, are central to bone resorption. Through the secretion of enzymes, they degrade the bone matrix, releasing essential minerals such as calcium and phosphate into the bloodstream, a process critical for mineral homeostasis. Osteoclasts adhere tightly to bone surfaces, creating a specialised resorption compartment where their breakdown activity is localised. The regulation of osteoclast activity is tightly controlled by signalling molecules, including RANKL (receptor activator of nuclear factor κB ligand), the major activator of osteoclastogenesis, and osteoprotegerin (OPG), which prevents excessive bone resorption.[1]

Osteocytes

The most prevalent cell type within mature bone, osteocytes originate from osteoblasts that become encased in the bone matrix. These cells play a crucial role as mechanosensors, detecting mechanical strain and directing remodelling in response to changing loads. Through an extensive canalicular network, osteocytes extend dendritic processes that facilitate communication with other bone cells and enable nutrient exchange. Osteocytes also release signalling molecules such as sclerostin, which modulates osteoblast activity and bone formation rates, underscoring their regulatory role in bone metabolism.[1] They are also the primary source of fibroblast growth factor-23 within bone, which is a potent regulator of renal phosphate transport.

Lining cells

Bone-lining cells are quiescent cells that form a protective layer over bone surfaces. Originating from pluripotent osteoprogenitor cells (like osteoblasts), they prevent unnecessary attachment of osteoclasts, hence playing a protective role in preserving bone structure.[1] While generally inactive, they can be activated to form new bone.

Together, these four cell types coordinate to ensure the constant adaptation and renewal of bone, a process compromised in disorders such as osteoporosis, where an imbalance in resorption and formation leads to bone loss and increased fracture risk.

Bone extracellular matrix

The bone extracellular matrix (ECM) is a complex, three-dimensional structure secreted by cells into the extracellular environment. Bone ECM comprises proteins and polysaccharides that provide structural support and elasticity to bone tissue. This matrix is in constant flux, adapting in response to cellular signals, growth factors, and local

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environmental conditions, including pH changes, to maintain tissue development, function, and homeostasis. Bone ECM is composed of both organic (40%) and inorganic components (60%), with its composition varying according to factors such as age, sex, and overall health. The inorganic portion predominantly contains calcium hydroxy-apatite along with trace elements, whereas the organic ECM is more intricate, mainly comprising type I collagen (90%) and a smaller fraction of non-collagenous proteins (10%). Osteoblasts synthesise the organic ECM, which later undergoes mineralisation, solidifying the bone structure.[3]

Importantly, the ECM endows bone with structural flexibility, balancing rigidity with resilience.[4]

Beyond its structural roles, the ECM actively influences bone cell regulation. It modulates the activity and differentiation of osteoblast-lineage cells – including progenitor cells, mature osteoblasts, and osteocytes – and osteoclast-lineage cells, encompassing both precursors and mature osteoclasts. This matrix also facilitates cellular communication between these opposing cell types, underscoring its role as a mediator in bone remodelling and tissue adaptation.[4]

Bone modelling and remodelling: the processes

Bone modelling and remodelling are essential processes through which the skeleton undergoes construction and reconstruction, ensuring its mechanical competence and resilience. While remodelling involves replacing old or damaged bone with new bone at the same location, modelling brings about architectural changes in bone shape and size by altering specific skeletal sites.[5]

Bone remodelling follows a cyclical sequence within the basic multicellular unit, a coordinated network of osteoclasts, osteoblasts, and a capillary blood supply. The cycle comprises five distinct but overlapping stages: activation, resorption, reversal, formation, and termination. Together, these stages enable continuous bone renewal and calcium homeostasis without altering overall bone morphology.[6]

In contrast, bone modelling, which initiates during early skeletal development, modifies bone shape and size. This process requires the spatial separation of resorption and formation activities; bone is removed from one site and deposited at another, allowing the skeleton to adapt to changes in body size and load-bearing demands. An example of modelling is the preservation of skeletal shape during linear growth, which maintains the structural balance needed for effective movement and load distribution.[6]

Under normal physiological conditions, bone mass and bone mineral density are sustained through a balance between osteoblast-mediated bone formation and osteoclast-driven bone resorption. This balance is finely regulated by a network of cytokines, which mediate cellular communication between osteoblasts and osteoclasts. Pro-inflammatory cytokines such as interleukins (ILs), and tumour necrosis factors (TNFs) play a central role in sustaining the equilibrium of bone turnover, enabling healthy bone maintenance. Disruptions in cytokine signalling can disturb this balance, leading to bone diseases such as osteoporosis, where excessive resorption undermines bone density and structural integrity.[7]

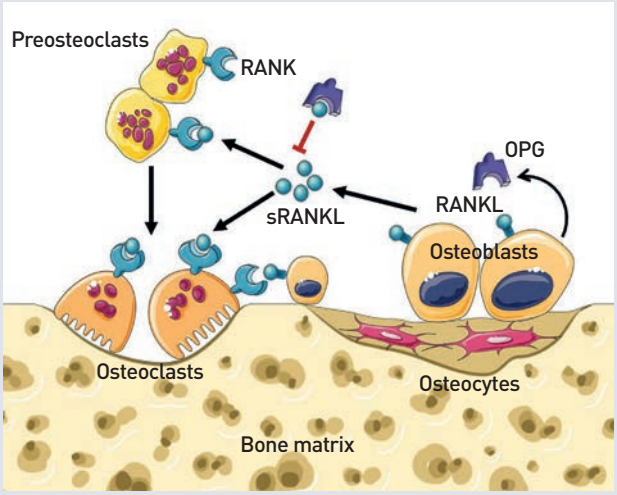
Bone modelling and remodelling pathways also serve as drug targets to treat diseases such as osteoporosis,[8] and therapeutic management is discussed in more detail later in this handbook.

Disruptions in osteoporosis

Osteoporosis is a progressive skeletal disorder marked by reduced bone mass and deterioration of bone microarchitecture, leading to increased fragility and →

FIGURE 1

Bone remodelling interactions



Osteoblasts express soluble and membrane-bound RANKL which binds to RANK in the membrane of osteoclast precursors. RANK signalling activates the differentiation towards osteoclasts. RANK signalling in osteoclasts promotes their bone resorptive activity and survival. Osteoblasts infiltrate into the cavities and synthesise the bone matrix. OPG is a decoy receptor produced by osteoblasts that binds RANKL, inhibiting the RANK signalling and regulating bone remodelling

fracture risk.[9,10] As previously discussed, bone is a dynamic tissue that remodels continuously through a balanced cycle of resorption and formation, driven by osteoclasts and osteoblasts. In osteoporosis, an acceleration and imbalance in this remodelling process favours resorption, leading to weakened bone structure.

The bone microarchitecture is disrupted in osteoporosis. It is associated with changes in the cancellous bone compartment, leading to thinning, morphological changes (the trabeculae becoming more rod-like in shape) and a decrease in their numbers, causing disconnections in the trabecular network.[11]

The cortical bone becomes porous and thin. Thinning from the endocortical side, widening of the void spaces in osteons (cortical porosity), and also a potentially diminished response of osteocytes and lining cells to mechanical loads leads to little or no modelling-based bone formation, hence not compensating for the bone loss induced by excessive remodelling.[11]

This disruption is often influenced by hormonal changes, especially the decline in oestrogen seen in postmenopausal women, which increases RANKL activity (see above).[12]

The RANK/RANKL/OPG signalling axis is fundamental in the molecular pathogenesis of osteoporosis.

Figure 1 shows some of the interactions in the normal bone remodelling process.

In inflammatory conditions, some ILs, such as Il-1 and IL-6, and TNFs (alpha) can further escalate osteoclast activity to excessive levels. This overactivity diminishes bone mass and compromises the microstructure, lowering bone density and integrity and ultimately increasing osteoporosis and fracture risk.

Key learning points

- Bone is a dynamic tissue, constantly undergoing remodelling to balance structural strength and metabolic function.
- Osteoclasts, osteoblasts, and osteocytes coordinate to maintain bone homeostasis, with each cell type playing specialised roles in bone formation and resorption.
- Bone extracellular matrix provides structural integrity and flexibility while interacting with bone cells to regulate remodelling and mineralisation.
- Bone remodelling is disrupted in osteoporosis, leading to decreased bone density, microstructural alterations and increased fracture risk, especially in postmenopausal women.
- Pro-inflammatory and anti-inflammatory cytokines influence the balance between bone resorption and formation, with cytokine dysregulation linked to increased osteoclast activity and the development of osteoporosis.

Conclusion

Bone biology encompasses a dynamic interplay of cellular and molecular processes that maintain skeletal structure and function throughout life. The balanced remodelling of bone, involving osteoblasts, osteoclasts, and osteocytes, is essential for both mechanical integrity and metabolic homeostasis. Factors such as hormonal shifts, cytokine networks, and ECM interactions contribute to this equilibrium, highlighting the adaptability of bone tissue to physiological demands. As seen in osteoporosis, disruptions to these processes lead to weakened bone and increased fracture susceptibility, underscoring the importance of proactive strategies in skeletal health. Continued exploration into the regulatory mechanisms governing bone remodelling offers promising pathways for therapeutic advancements that support lifelong skeletal health.

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Osteoporosis: burden and incidence

Osteoporosis can significantly impact quality of life, morbidity and mortality, and drain health and social care services. In this article, ts impact on the quality of lives of those affected, healthcare resources, the cost of social care, and the wider society is considered

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Osteoporosis represents a significant clinical, economic and societal challenge, and the prevalence and burden are anticipated to increase alongside an increasingly ageing population.

According to the International Osteoporosis Foundation, around one in ten (approximately 200 million) women aged 60 years worldwide are affected by osteoporosis. That proportion rises to 20% of women aged 70 and two-thirds of women aged 90.[1]

Disease epidemics

Scorecard for Osteoporosis in Europe (SCOPE) is an international project to determine the burden of osteoporosis across Europe.[2] The SCOPE panel was first established in 2010 and updated in 2021 and evaluates the information regarding osteoporosis in 29 countries through a series of structured questionnaires covering 27 European countries, the UK and Switzerland.[2]

In 2019, it was estimated that 25.5 million women and 6.5 million men in Europe had osteoporosis – equating to 5.6% of the total population. Of those aged over 50 years, 22.1% of women and 6.6% of men had the disease.[2]

In the EU, based on data from 2010, approximately 22 million women and 5.5 million men between the ages of 50 and 84 years have osteoporosis. The number of men and women with osteoporosis is projected to rise by 23% to 33.9 million by 2025.[1]

Germany is thought to have the highest number of people with osteoporosis in Europe – approximately one million men and four million women. The prevalence of osteoporosis among males aged 50 years and over in Europe was approximately 5.7% in Slovakia, rising to around 6.9% in Greece, Italy, and Sweden. For women, the proportions were 19.3% in Bulgaria and 23.4% in Italy.[3]

In terms of prevalence by age group, the highest prevalence for women occurs in the group aged 75–79 years at about 3.9 million, while for men, the highest number with the disease – around 0.8 million – is seen in those aged 60–64 years.[3]

Patients may only be aware they have osteoporosis once they experience a fragility fracture. Low bone mineral density may be associated with fractures of any kind. However, fractures of the spine, hip, forearm and proximal humerus are more common in patients with osteoporosis, whereas other type of fractures, such as of the ankle, hands, feet and skull are not as strongly associated with reduced bone mineral density but rather with high impact trauma.[4]

The risk of developing osteoporosis and fractures is greater than that associated with other common major diseases. For example, among white women, the lifetime risk of hip fracture is one in six compared with a one in nine risk of developing breast cancer.[1]

The SCOPE 2021 summary reports that more than 23 million men and women in the EU are at high risk of osteoporotic fractures, with 4.28 million fragility fractures occurring annually in 2019. This figure is expected to rise to 5.34 million by 2034. By then, the UK is expected to have around 665,000 fragility fractures, which is only exceeded by 701,600 in Italy and 966,800 in Germany.

Those countries also saw the greatest increase in absolute numbers of women estimated to have osteoporosis between 2010 and 2019: Germany, 153,200; UK, 141,700; and Italy, 129,700.[2]

The incidence of hip fracture has been highest among people of European ancestry (Northern European in particular) and lowest in East Asian populations. The reason is unknown and not explained by differences in bone mineral density. It could be related to changes in lifestyle, urbanisation, obesity, birth period cohort effects and consequences of screening.[5]

Patient burden

Osteoporotic fractures have severe long-term consequences.[4]

More significant impairments in functional status and quality of life are associated with hip fractures than other types of fractures. Vertebral fractures, for example, can cause significant pain or may be associated with minimal symptoms and be detectable only by scanning.[4]

In a large cohort of more than 300,000 Danish adults aged 50 years and older followed for a median of 6.5 years, fractures significantly increased the risk of mortality. The highest risk was observed in individuals with hip fractures, particularly those with other comorbidities, such as malignancy, where the one-year excess mortality ranged between 30% and 40.8%, or cardiovascular disease and diabetes, with one-year excess mortality for hip fractures in these groups ranging from 20% to 30%.[6]

While hip fractures had the most profound effect on mortality, the study found that even minor fractures, such as rib fractures, were associated with a notable increase in mortality, even in patients without comorbidities. For instance, in the low-multimorbidity cluster, rib fractures had a one-year excess mortality of 3.08% in men and 3.21% in women.

This study further demonstrated that fractures, even those that might be considered minor such as rib fractures, can →

result in significant mortality, particularly when combined with chronic conditions such as cardiovascular disease or malignancy.[6]

In terms of quality of life, patient burden can be assessed using quality-adjusted life years (QALYs). QALYs lost per capita due to fragility fractures in 2017 ranged considerably across the five largest EU countries and Sweden (EU6), from 2.1 per 1000 people in France and up to 4.2 per 1000 people in Sweden. The total health burden attributed to fragility fractures in the six countries in 2017 was 1.02 million QALYs.[4]

An analysis of 1,822 fractures (57% minor non-hip, non-vertebral (NHNV), 26% major NHNV, 10% spine and 7% hip fractures) among 50,461 women found that spinal fractures had the most significant detrimental effect on EuroQol EQ-5D summary scores, causing problems with self-care, activities and pain and discomfort.[7] Physical function and health status deteriorated most in women with spine or hip fractures.[7]

Fractures of the spine or hip account for around 30% of the deaths that occur after such events. In 2019 in Europe, approximately 248,487 fractures were causally related to fatalities. Hip fractures were associated with almost half (49%) of fatalities attributed to fractures.[2] Longer time to surgery (more than 24–48 hours after the fracture) is a significant predictor of early mortality; it is also associated with a more extended hospital stay.[3]

The risk of mortality associated with fracture is highest in the first five years after the fracture, although for hip fractures, the risk remains elevated for the first ten years.

For example, an Australian study of individuals aged 60 years and over found mortality rates among people with fractures of 7.8 per 100 person-years for women and 11.3 per 100 person-years for men. That compared with mortality rates for the population aged 60 years and older as a whole of 4.3 per 100 person-years for women and 5.5 per 100 person-years for men.[8]

Hip fracture and the surgical treatment needed to repair the damage put frail older people at risk of other problems such as deterioration of other chronic diseases as well as complications such as anaemia, pneumonia, delirium, urinary tract infection and thromboembolic events.[3]

Between 40% and 60% of hip fracture survivors are likely to recover their pre-fracture level of mobility. Up to 70% of people

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may regain their pre-fracture level of independence for composite measures of basic activities of daily living (ADL). However, only 50% or fewer are likely to regain their pre-fracture level of independence in instrumental activities of daily living (IADLs).[3]

People who do recover their ADL or IADLs usually do so within six months of discharge but some may take up to 11 months. In Western countries, 10%–20% of people with a hip fracture are institutionalised within 6–12 months of having a fracture.[3]

Differences in fracture rates and probabilities

Substantial differences in fracture rates between countries have been observed. Lorentzon et al report that the age-standardised annual hip fracture rate per 100,000 women is the highest across Scandinavia.[4]

Differences in bone mineral density cannot explain the significant difference in incidence between countries; proposed contributing factors include differences in body composition, levels of physical activity, socioeconomic status, calcium intake and differences in sunlight exposure.[4]

The lifetime probability of women having a hip fracture varies considerably from one European country to another. For example, the risk is 7% in Romania and 25.1% in Sweden, with an average in Europe of 5.7% for men and 15% for women.[2]

Economic and societal burden

The disability burden of osteoporosis in terms of disability-adjusted life years (DALYs – a measure of years of life lost and years lost to disability) ranks higher than several other common chronic diseases such as ischaemic heart disease, dementia and lung cancer.[2]

In the EU6, 2.6 million DALYs resulted from fragility fractures in 2016. For every 1000 people, the average number of years lost to disability was 15.1 compared with 5.5 years of life lost.[4]

With an ageing population, the social burden of osteoporosis is expected to continue to increase. A Norwegian study suggests that health lost to hip fractures will increase from 32,850 DALYs in 2020 to 60,555 DALYs in 2040, with an increase in costs associated with the disease of around 65%.[4]

The direct cost of incident fractures in Europe was calculated at €24.6 billion in 2010 and €36.3 billion in 2019, with long-term disability costs thought to be €10.7 billion in 2019, rising to €19 billion in 2019. Hip fractures had the most significant impact, accounting for 54% of the direct costs associated with the disease.[2]

The cost of osteoporosis to individuals in Europe in 2019 ranged from €18 in Romania to €403 in Switzerland, with an average cost across Europe in 2019 of €109.12 – 27.2% higher than €85.77 in 2010.[2]

The greatest disutility and highest costs are associated with hip fractures. Globally, the healthcare and social costs in the first year after a hip fracture amount to an annual sum of US$ 43,669 for each hip fracture – including inpatient costs of US$13,331 and rehabilitation care costs of US$12,020.[4]

In the EU6, the total number of fractures is projected to rise by 23.3% from 2.7 million in 2017 to 3.3 million in 2030. That will equate to a 27% increase in costs to €47.4 billion by 2030.[4]

In Europe, the cost of assessment and treatment for people with osteoporosis was estimated to be €2.1 billion in 2010, which rose to €1.6 billion in 2019.[2]

Length of stay in hospital due to hip fractures varies in the EU6 from 11.6 days in Sweden to 20.5 days in the UK.[4]

Key learning points

- In the European Union, based on data from 2010, approximately 22 million women and 5.5 million men between the ages of 50 and 84 years have osteoporosis.
- The number of men and women with osteoporosis in Europe is projected to rise by 23% to 33.9 million by 2025.
- Patients may not be aware they have osteoporosis until they experience a fragility fracture.
- The lifetime probability of women having a hip fracture varies significantly from one European country to another. For example, the risk is 7% in Romania and 25.1% in Sweden, with an average in Europe of 5.7% for men and 15% for women.
- Fractures of the spine or hip account for around 30% of the deaths that occur after such events.
- Hip fracture and the surgical treatment needed to repair the damage put frail older people at risk of other problems, such as the deterioration of other chronic diseases as well as complications such as anaemia, pneumonia, delirium, urinary tract infection and thromboembolic events.
- The direct cost of incident fractures in Europe was calculated at €24.6 billion in 2010 and €36.3 billion in 2019 with long-term disability costs thought to be €10.7 billion in 2019 rising to €19 billion in 2019.
- In the five largest European countries, along with Sweden, the total number of fractures is projected to rise by 23.3% from 2.7 million in 2017 to 3.3 million in 2030. That will equate to a 27% increase in costs to €47.4 billion by 2030.

Conclusion

As we have seen, osteoporosis presents a significant burden, not only to those who have the disease but to the health services charged with managing patients, social care services that deal with the consequences of the disease and society as a whole that has to bear the burden of the impact the disease has, including disability and reduced quality of life.

Osteoporosis is common and the proportion of people affected rises with age. It affects men as well as women. It impairs quality of life and impacts a wide range of aspects of everyday life, including self-care and activities, as well as pain and discomfort.

For a disease that often becomes apparent only when a significant event such as a fracture happens, it is one that perhaps should be given greater priority in terms of earlier identification through awareness raising and screening.

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Risk factors for osteoporosis

Osteoporosis is becoming increasingly more common due to population ageing. Numerous risk factors have been described, and vigilance can improve fracture prevention. This article reviews the risk factors for osteoporosis, categorised into non-modifiable and modifiable factors

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Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fracture.[1] The epidemic of fragility fracture is considerable, affecting one in three women and one in five men over the age of 50 years in the Western world.[2–4] Understanding the risk factors for osteoporosis is crucial for prevention, early diagnosis, and effective management.

Risk factors

Table 1 summarises the non-modifiable and modifiable risk factors for osteoporosis.

Non-modifiable risk factors

Age

Age is a significant risk factor for osteoporosis. Bone mass peaks in the third decade of life and declines thereafter.[5] The risk of osteoporosis increases with age, with a more rapid bone loss observed in women after menopause and fracture risk is much higher in the elderly than in the young.[6]

Gender

Females are at a higher risk of developing osteoporosis than males. This is partly due to the fact that women have smaller bones and lower peak bone mass. They experience a rapid loss of bone mass during menopause that continues, albeit more slowly, for many years thereafter.[7]

Ethnicity

Ethnicity plays a role in osteoporosis risk. Caucasian and Asian women have a higher risk of developing osteoporosis compared to African American and Hispanic women.[8]

Genetics and family history

Genetic factors contribute to the risk of osteoporosis, with heritability of bone mineral density (BMD) estimates ranging from 50% to 85%.[9] A family history of osteoporosis or fragility fractures is a strong predictor of future fracture risk.[10]

Menopausal status

Oestrogen deficiency due to menopause increases bone resorption and rapid bone loss.[11] Early menopause (before age 45) and surgical menopause increase the risk of osteoporosis.[12]

TABLE 1

Risk factors for osteoporosis

Non-modifiable risk factors	Modifiable risk factors
• Older age	• Bone mineral density
• Gender	• Diet and nutritional factors
• Ethnicity	• Sedentary lifestyle
• Genetics and family history	• Body weight
• Menopausal status	• Smoking
• Prior fracture	• Alcohol consumption
	• Certain medications
	• Certain medical conditions

Modifiable risk factors

Bone mineral density

It is debatable to include BMD as a risk factor for osteoporosis because it is part of the disease definition, as it is both a risk factor for fracture and a diagnostic tool. Many cross-sectional and prospective population studies indicate that the risk for fracture increases by a factor of 1.5–3.0 for each standard deviation decrease in BMD.[13]

Diet and nutrition

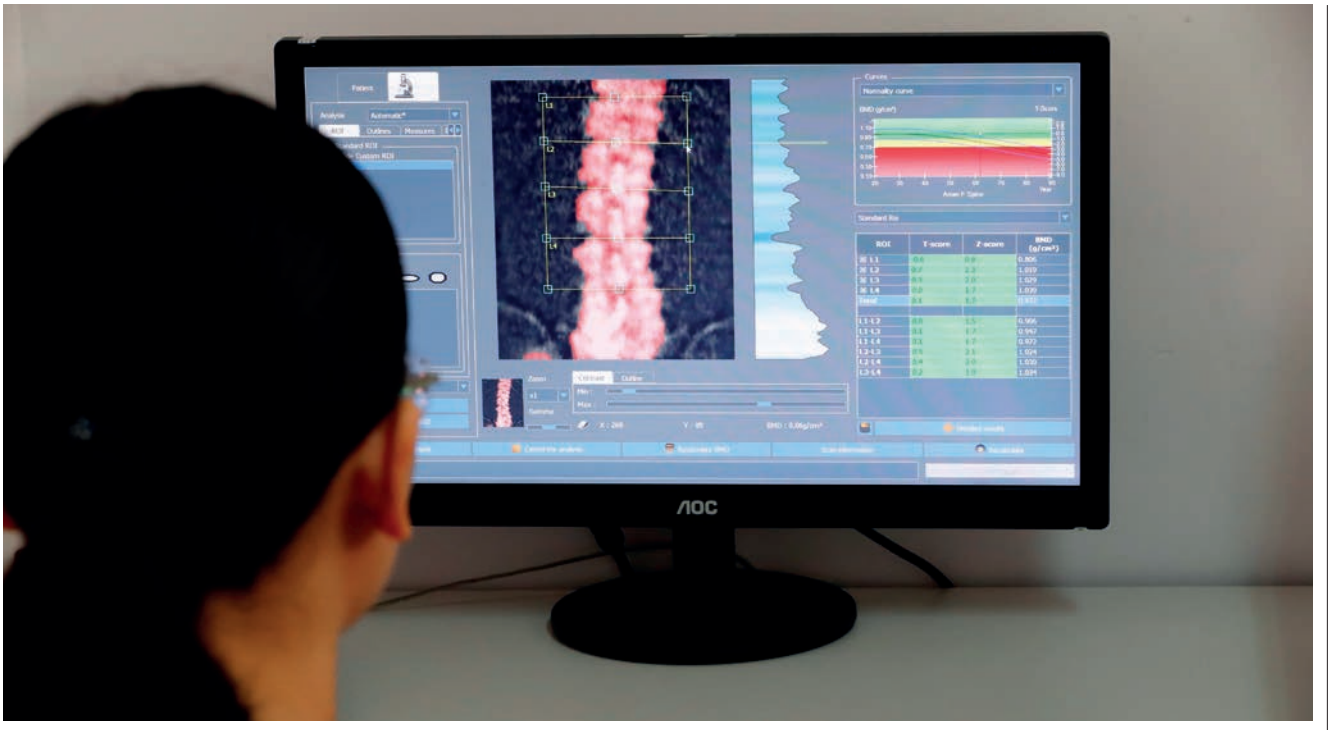
• **Calcium and vitamin D:** Low dietary intake of calcium and vitamin D is associated with an increased risk of osteoporosis. These nutrients are essential for bone health, and inadequate intake can reduce BMD.[14] The strength of this risk factor, however, is less important than many others, like age and endocrine factors. Also, calcium and vitamin D deficiencies may lead to osteomalacia rather than pure osteoporosis.

• **Protein:** Both low and high protein intake can negatively affect bone health. Low protein intake can reduce BMD, while high protein intake can increase calcium excretion.[15]
A proteomic risk score has been shown to predict hip fracture risk in a large dataset of patients with fracture and controls.[16]

• **Other nutrients:** Deficiencies in vitamin K, magnesium, and vitamin B12 have also been linked to an increased risk of osteoporosis.[17]

Low mechanical loading

A sedentary lifestyle is a risk factor for osteoporosis. Regular weight-bearing and resistance exercises can increase BMD and reduce the risk of fractures. Beyond physical activity and sport, prolonged immobility, e.g., spinal cord injury, space travel, Parkinson's disease, stroke and muscular dystrophy lead to rapid bone loss.[18]



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Body weight

Low body weight (body mass index <19 kg/m^2) is associated with an increased risk of osteoporosis, and hence fracture. Lower body weight means less mechanical loading on bones, which can lead to reduced BMD.[19]

Smoking

Smoking is a well-established risk factor for osteoporosis. It can decrease bone formation, increase bone resorption and impair calcium absorption.[20]

Alcohol consumption

Excessive alcohol consumption can negatively affect bone health by inhibiting bone formation and increasing bone resorption.[21]

Medications

Certain medications can increase the risk of osteoporosis. These include:

- **Glucocorticoids:** use can lead to significant bone loss and increased fracture risk,[22] proportionally to the dose and duration of therapy. These drugs sharply decrease bone formation and also increase bone resorption.
- **Proton pump inhibitors (PPIs):** long-term use of PPIs has been linked to an increased risk of osteoporosis and hip fracture.[23]
- **Antidepressants**: selective serotonin reuptake inhibitors have been associated with reduced BMD and increased fracture risk.[24]
- **Aromatase inhibitors:** by reducing the concentration of residual oestrogen, they increase bone loss and the risk of fracture in women who receive this class of drug as an adjuvant therapy for breast cancer.[25]

Medical conditions

Several medical conditions can increase the risk of osteoporosis, including:

- **Endocrine disorders** such as hyperthyroidism, hyperparathyroidism, and Cushing's syndrome. Untreated hypogonadism in men and women, e.g., premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism, androgen deprivation therapy in men with prostate cancer. Osteoporosis in anorexia nervosa is compounded by nutritional deficiencies.[26]
- **Type 1 and type 2 diabetes** have emerged as significant causes of osteoporosis ('diabetoporosis'). Type 1 patients tend to have lower BMD than controls, whereas type 2 patients have higher BMD – but deteriorated bone properties – compared with healthy individuals.[27]
- **Gastrointestinal disorders** such as coeliac disease, inflammatory bowel disease, and gastric bypass surgery, can lead to malabsorption of nutrients essential for bone health.[28]
- **Inflammatory diseases** such as inflammatory bowel diseases, chronic obstructive pulmonary diseases, rheumatoid arthritis, spondyloarthritis and HIV, generally uncouple bone turnover and lead to accelerated bone loss.[29]
- **Chronic kidney disease (CKD)** patients sustain more fractures, especially hip and vertebra fractures. Bone fragility stems from complex mechanisms, including secondary hyperparathyroidism, adynamic bone disease or osteomalacia.[30]

Risk factors for secondary osteoporosis

Secondary osteoporosis occurs due to an underlying medical condition or medication use. It accounts for up to 30% of cases of osteoporosis in postmenopausal women and up to 50% in men. The risk factors for secondary osteoporosis include various medical conditions and medications, as discussed above.[26]

Risk assessment tools

Several tools have been developed to assess the risk of osteoporosis and fractures, to determine which patients may receive prevention or treatment. The most widely used is the Fracture Risk Assessment Tool (FRAX), developed by the World Health Organization. FRAX estimates the ten-year probability of hip fracture and major osteoporotic fracture based on clinical risk factors, with or without BMD. →

The Fracture Risk Assessment Tool (FRAX) was developed via systematic meta-analysis of primary data from nine geographically spread cohort studies and validated in a further 11 cohorts and was published in 2008.[31]

Key principles were used to identify variables to be included in the FRAX algorithm including:

- The variable should be intuitively linked to fracture
- The variable should be readily clinically available
- The variable should be (at least partly) independent of BMD
- The variable should be associated with a risk which might be reversed by pharmacological therapy.

The clinical parameters chosen were age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoid usage, rheumatoid arthritis, secondary causes of osteoporosis, alcohol consumption and BMD (although this can be excluded if BMD measurement is not available). The output is a ten-year probability of a major osteoporotic fracture (clinical spine, proximal humerus, distal forearm or hip fracture) and a ten-year probability of hip fracture.[31]

Other risk assessment tools include the Garvan Fracture Risk Calculator, which estimates the five-year and ten-year risk of fracture (its main difference to FRAX is that the Garvan includes the risk of falls), and the QFracture algorithm, which estimates the ten-year risk of osteoporotic fracture.

Preventive strategies

Understanding the risk factors for osteoporosis is crucial for prevention and management. Lifestyle modifications, such as regular exercise, a balanced diet rich in calcium and vitamin D, smoking cessation, and limiting alcohol intake, can help prevent osteoporosis. For those at high risk, pharmacological interventions may be necessary to prevent fracture.[10]

Of note, falls represent an important risk factor for fracture but not for reduced bone mass, i.e., osteoporosis, but implementing fall prevention strategies should be considered.

Furthermore, previous fractures are a significant risk factor for subsequent fractures, signalling an existing osteoporotic condition. It is crucial to look for and account for those previous fractures to prevent future events.[32]

At least three large randomised trials have shown that by monitoring several of the risk factors described above in primary care, individuals at the highest risk can be identified and preventive therapies initiated, thus reducing the burden of fractures, especially those of the hip.[33]

Key learning points

- Age and hypogonadism are strong risk factors for osteoporosis.
- Risk factors for osteoporosis are generally easy to identify by history-taking.
- Some risk factors are modifiable; some others are not.
- Peak bone mass, responsible for osteoporosis if it is inadequate, is mainly genetically determined.
- Many endocrine or inflammatory diseases increase the risk of osteoporosis.

Conclusion

Osteoporosis is a multifactorial disease with numerous risk factors, which fall into non-modifiable and modifiable categories. Understanding these risk factors is essential for osteoporosis prevention, early diagnosis, and effective management. Healthcare providers should assess patients' risk factors and provide personalised recommendations for preventing and managing osteoporosis. Public health initiatives should focus on educating the population about the risk factors and preventive strategies for osteoporosis.

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Screening and diagnosis: a concise guide

Here, we outline the basis for screening, diagnosis, and risk assessment of osteoporosis and propose a three-step process for assessing older adults. Adoption and adaptation of this process supported by national policy is urgently needed to mitigate the rapidly rising number of osteoporotic fractures worldwide and reduce the costs and harms associated with overdiagnosis and inappropriate treatment

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Osteoporosis is the most prevalent skeletal disease worldwide. Failure to attain or loss of skeletal mass and quality results in weak bones, leading to fractures. Bone fractures are a leading cause of morbidity worldwide today. Fracture incidence, hospital admissions, morbidity, mortality and healthcare costs in Europe and North America are rising, and on par with other non-communicable diseases such as cardiovascular disease and cancer.[1–5]

A report from the Global Burden of Disease study group estimated that almost 200 million fractures occurred worldwide in 2019, while nearly half a billion people are living with the consequences of fractures, numbers of which have almost doubled over the past 30 years.[2] Because the incidence rises with age, it is reasonable to assume the majority are osteoporosis-related.[2]

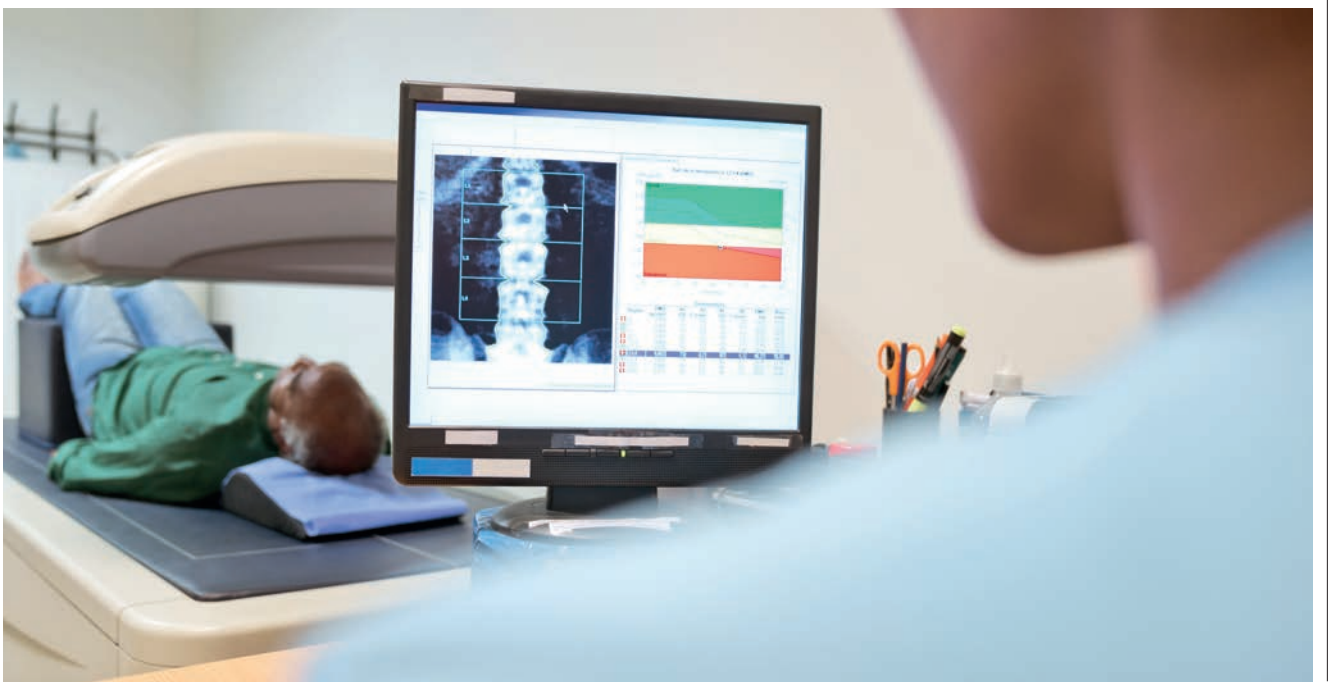
Because vertebral fractures are grossly underestimated and are the most common site of fracture,[6] these numbers probably represent a conservative estimate. In 2019, more than 4 million people in Europe suffered an osteoporotic fracture, accounting for around 250,000 deaths and direct healthcare costs of almost €60 billion.[4] Data from North America are similar, while estimates from other regions are more difficult to harmonise.[3] Current projections suggest more than half of the world's hip fractures will occur in Asia by 2050.[7]

Diagnosing osteoporosis

Historically a diagnosis of osteoporosis was based on the presence of fractures, or radiologic changes described as 'indistinct and subjective'.[8] Quantitative analysis of cortical bone on radiogrammetry studies were introduced, enabling not only diagnosis but also grading of severity.[9] Later methods include nuclear medicine and ultrasound technologies, but Dual-energy X-ray Absorptiometry (DXA) was a significant advancement in the field.[10]

Today, a number of methods exist, including qualitative and quantitative imaging of bone, non-invasive and invasive assessments of bone ultrastructure, and resistance to bending and indentation.[5,7]

The most widely used methods for clinical diagnosis are fractures and densitometry.[3,7] →



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Fractures

Osteoporosis can be diagnosed in the setting of a fragility fracture, particularly of the proximal femur or spine.[3,5,7]

A fragility fracture can be thought of as one which occurs from a force considered insufficient to fracture a healthy bone. These represent this disease's clinical events or consequences.[3] A global consensus representing 14 international professional medical societies recognised the importance of diagnosing osteoporosis in the setting of a fracture of the forearm, hip, humerus, pelvis, ribs, tibia and vertebrae.[3] Other fractures may be osteoporosis-related, but the relationship between bone mineral density and osteoporosis is unclear. Thus, all patients should be considered to have osteoporosis following fracture, and the question is not 'Do they have it?' but 'Why?' and 'How to manage them?'

Such patients should be assessed for modifiable and non-modifiable risk factors and considered for appropriate pharmacologic intervention and fall prevention.[3–5] Unfortunately, despite overwhelming evidence showing that diagnosis and treatment are the most effective ways to reduce subsequent fracture risk,[3–5,11] there is a considerable gap between the evidence and recommended management and what is taking place in practice.[11–14] International standards for fracture liaison services are widely accepted, but considerable gaps remain,[12,14]

While such services address care of the fracture patient and secondary prevention, which are both important,[3,5,11–14] a more fundamental approach is primary prevention delivered via evidence-based, planned and resourced screening programmes.[15]

Bone densitometry

Bone densitometry has been used for more than 100 years, but the introduction of DXA technology in 1987 ushered in a new era.[10]

Several years later, a group of experts working with the World Health Organization (WHO) introduced diagnostic criteria for postmenopausal osteoporosis and low bone mineral density (BMD).[16] Although these criteria were intended to support classification for epidemiology studies of populations not individuals, and were published with several caveats, their application to individuals was rapidly implemented and encouraged and endorsed by clinical guidelines.[3,5,7]

The International Society for Clinical Densitometry (ISCD) expounded and added clarifications to unclear areas, and established criteria for the diagnosis in men, younger women and children.[17] The ISCD regularly updates clinical practice guidance, teaches courses and establishes criteria for new developments in the field and technologies.[17] Today, various other methods, such as ultrasound and computerised tomography, are used to assess the risk of fracture, diagnose low BMD or osteoporosis and monitor the effectiveness of interventions.[7,18]

DXA

DXA is a test that estimates bone strength by measuring BMD. Although BMD is just one important characteristic of bone, DXA performs remarkably well in identifying those at risk for fracture and monitoring those on osteoporosis treatment.[19,20] BMD is expressed in g/cm^2, and also as standard deviations from the mean of a young, healthy reference population (the T-score), and/or an age, gender, and ethnicity-matched reference population when available (the Z-score).[17–19]

The most widely recommended reference population for T-score calculation is the NHANES III white female 20–30-year data, which may not be appropriate for all populations, particularly where good reference data exist. Furthermore, NHANES III only included hip BMD.[18–20]

A 2016 best practice guide from the ISCD highlighted seven minimum criteria for the correct performance of DXA and seven minimum criteria for interpreting and reporting DXA studies.[21] This has now been updated in a more extensive document, endorsed by 14 international professional societies.[20]

According to the WHO criteria, which the ISCD say apply to peri- or postmenopausal women and men aged 50 years and older, a T-score of ≤-2.5 can be considered osteoporotic, a T-score between -1.0 and -2.5 as 'low BMD', and a T-score of -1.0 or higher as normal BMD. Persons with a T-score ≤-2.5 with a prevalent fracture are considered 'severe' osteoporosis.3[17–21] By contrast, for premenopausal women, men <50 years of age and children, a Z-score of ≤-2.0 may be considered as 'low BMD for age'. However, a diagnosis of osteoporosis should not be based on densitometric criteria alone in these populations.[3,17–21]

Patient recommendations

DXA testing is recommended for all men and women with a fragility fracture, for others with major risk factors or deemed high-risk for fracture, or where the results of the DXA scan may influence treatment.[17] Additional testing, such as further imaging and blood tests, may be required depending on the findings of an appropriate history and physical examination.[3] Screening DXA scans are considered by some to be controversial, though the evidence clearly shows screening is important and clinically and cost-effective for primary prevention.[5,7,10,11,17,18]

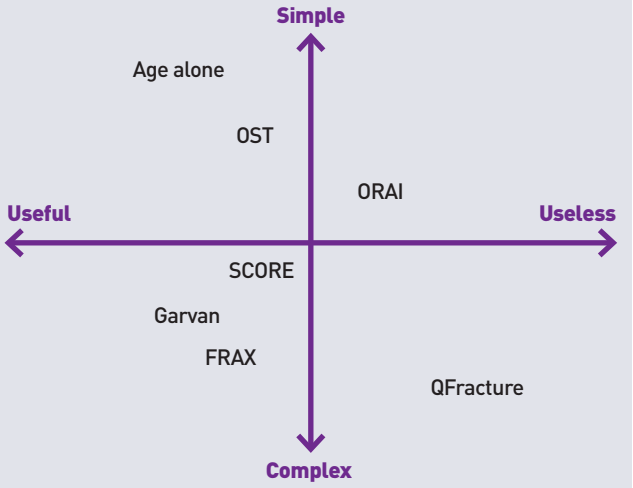
A number of clinical algorithms have been used to help clinicians decide who is most likely to need a DXA scan or have osteoporosis. In contrast, others help determine the risk of future fracture, with or without the inclusion of DXA results,[22] conceptualised in Figure 1.

Limitations

While densitometric criteria are very helpful for classifying groups of people as 'osteoporotic' or not, their performance for individuals is not perfect because most osteoporotic fractures occur in adults whose T-score is > -2.5.[3,18] Studies

FIGURE 1

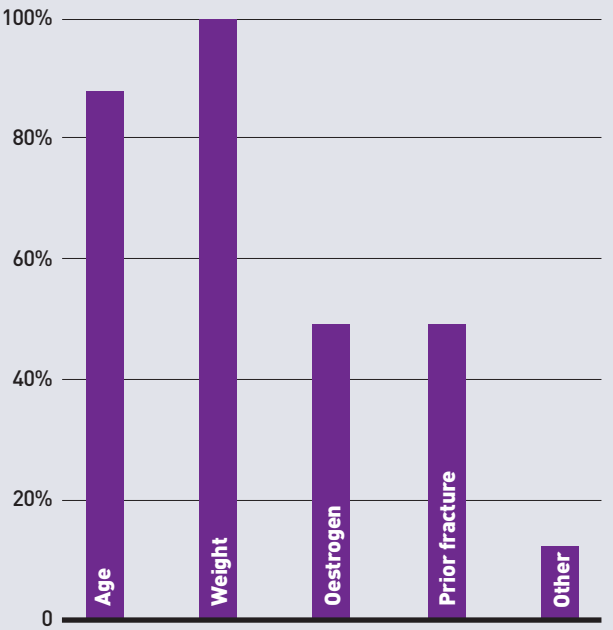
Conceptualisation of various osteoporosis clinical assessment tools

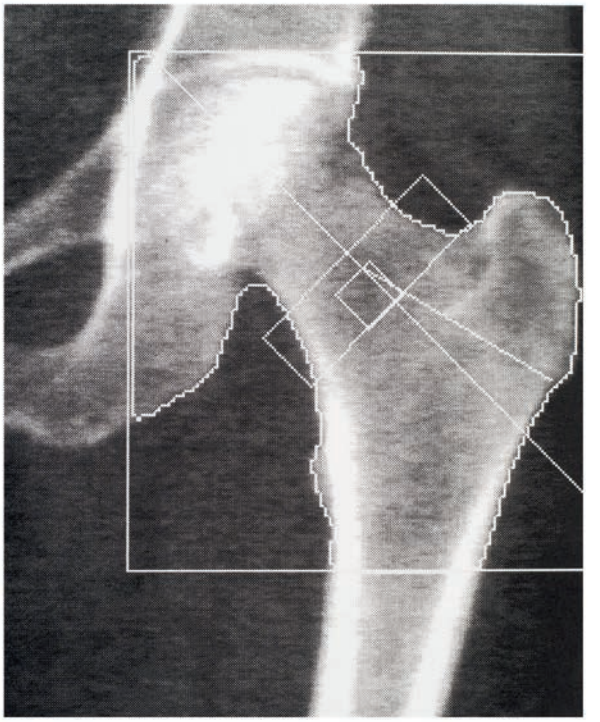


Note: The particular location any tool included on this plot should not be deemed to be a judgement of their validity, rather one that is more arbitrary to highlight the concept.

FIGURE 2

Prevalence of clinical factors included in algorithms to identify people with low BMD or osteoporosis[7,22]





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suggest these criteria thus have a sensitivity of <50%, but specificity of >80%.[18] A study of vertebral fractures in a nationally representative US population shows that the mean T-score among those with fractures was -0.9.[23]

In this study, 70% of those with fractures had a T-score that was >-2.5, while one in three adults with fractures aged 50–64 years had normal BMD and one in four adults aged 65 years or older.[23]

Vertebral fracture assessment (VFA) scans

VFA scans are newer technologies used to identify the presence of vertebral fractures at the time of DXA scanning,[18,20] potentially changing the diagnosis to one of osteoporosis or identifying those with one or more fractures, thereby indicating a worse prognosis and greater likelihood of further fractures.[18,20,24]

For example, a person with a T-score of -2.4 might be classified as 'low BMD', but the difference in fracture risk is minimal compared to a person with a T-score of -2.6 who might be considered 'osteoporotic'. However, if the former has one or two vertebral fractures on their VFA scan, then they should be considered as having a clinical diagnosis of osteoporosis, and they have a much greater likelihood of fracture over the next year or two than the person who is regarded as having a densitometric diagnosis of 'osteoporosis'.[24]

Screening: not the same as early diagnosis

Screening is a process to identify asymptomatic people at increased risk of a disease before it occurs. This enables patients and their clinicians to intervene to reduce their chance of developing a disease, event, or the severity of illness if it does occur.[15] Screening is not the same as early diagnosis.[7,15]

Effective screening programmes represent a process to identify those at risk while minimising the harms and costs associated with overdiagnosis and ineffective interventions.[15] Testing people with fractures is therefore not screening; instead, it is assessing their prognosis or monitoring for intervention.[7] Unfortunately, loose use of the terms 'screening' and 'testing' in the medical literature can lead to confusion, and some authors and papers use these terms interchangeably, even for those with fractures. Put another way, screening can identify those at risk before they fracture, a diagnosis can be made in those with fractures or using DXA among those without fractures, and their prognosis can be estimated following fracture.[7,10]

Screening standards and criteria

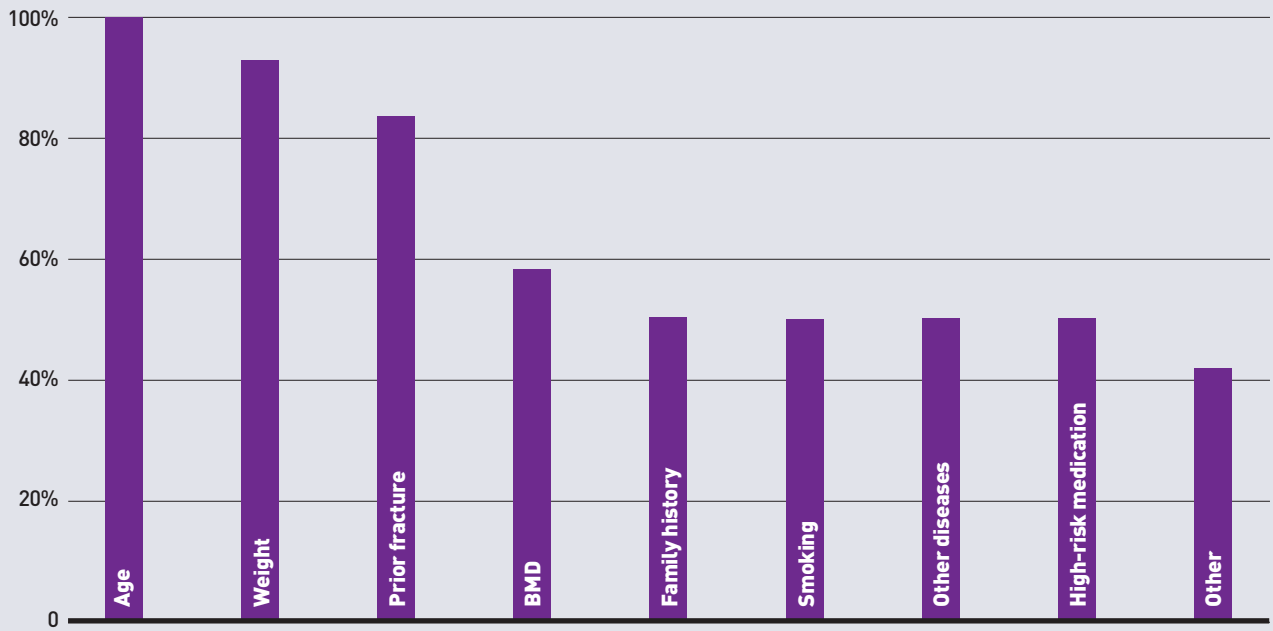
The WHO initially published a report in 1994 for screening postmenopausal women for osteoporosis[16] and later an extensive report which included men.[25] These detail the epidemiology and natural history of osteoporosis, describe analogies to other disease areas such as cancer and cardiovascular disease and propose standards for screening and diagnosis among those at risk.

The 1994 report proposed today's accepted standard: a T-score of <-2.5 as the diagnostic threshold for the diagnosis in postmenopausal women.[16] These criteria have been modified and improved by others, led by the ISCD, and a recent essential best practice guide is now published detailing who should be referred for DXA testing, how it should be done, how DXA testing should be reported and how to interpret the reports in clinical practice.[17,20,21] Age is the most widely cited criterion for deciding when to screen men and women,[3,7,17] but various clinical algorithms can help clinicians identify those most likely to have osteoporosis and, thus, whom to refer for a DXA scan.[7,22]

A systematic review suggests no one tool substantially →

FIGURE 3

Prevalence of clinical factors included in various fracture risk algorithms[7,22]



outperforms others.[22] Figure 2 shows age and weight are the most commonly used factors in these tools, while 50% include a prior fracture. Clearly, including people with a previous fracture is not screening but testing those who already have the disease.[3,7]

Screening recommendations and guidance

Today, major international organisations agree that screening postmenopausal women is appropriate and both clinically and cost-effective.[3,7,17] The majority recommend screening all women aged 65 years and older and younger women with major risk factors such as a family history of osteoporosis, corticosteroid use or rheumatoid arthritis.[3,7,17,20] There is less consensus for men, partly due to some ambiguity around the interpretation of the epidemiology and treatment effectiveness in men.[7,16,19,25,26] Most agree, however, that screening is appropriate as men make up between 20% and 30% of all fragility fractures,[3,7,17,25] but acknowledge some uncertainty around who precisely should be screened and what interventions might be used.[26] Guidelines recommend screening men aged 70–75 years and older and younger men with major risk factors, similar to postmenopausal women.[3,7,17,25]

Effectiveness of screening

The United States Preventive Services Task Force (USPSTF) has undertaken several comprehensive quantitative assessments of the effectiveness of screening.[26,27] In 2002, they elegantly presented the importance of choosing an appropriate age for screening.[26] The number of women aged 50 years and older (or men presumably) who needed to be screened to prevent one hip or one vertebral fracture is almost ten-fold higher than starting screening at age 65 years.[26] Addition of another risk factor, such as body weight, could substantially reduce this number.[26] Because overdiagnosis in younger, healthier people could be as problematic as underdiagnosis among older at-risk populations, this concept warrants serious consideration.[26]

Contemporaneously with the first USPSTF report, a group of researchers in Asia developed the Osteoporosis Self-Assessment Tool (OST).[28] This tool combines age and weight to help identify those most likely to have osteoporosis and has been widely validated among populations of both men and women.[28–31] Addition of this single factor could reduce the number of adults requiring a screening DXA by around 30% and OST perhaps outperforms more complex algorithms.[29,31] Access to quality DXA is a global problem,[32] and poor quality DXA services harm patients.[3,19] Critical appraisal of who should be screened and the application of a best practice framework to support it will enable the best use of available resources and reduce the cost and harm associated with a screening programme.[3,18,20,32]

Fracture risk assessment tools

While several algorithms are available to decide who should get a DXA scan, others are available to assess a person's fracture risk. It is important to remember these two purposes are not the same, which can be a source of confusion among clinicians.[7]

Figure 3 outlines some of the most frequently included factors in these algorithms, which can be as simple as age alone but possibly include up to 31 factors.[7,22] Similar to those for identifying people likely to need a DXA scan, age and weight are the most commonly included factors.

Interestingly, 80% include a prior fracture, suggesting these are more prognostic than risk-based,[7] while just over 50% include BMD, the best predictor of future fracture risk in people without prior fractures.[30]

Including BMD in fracture risk assessment is important because whereas treating postmenopausal osteoporotic

women with or without fractures is effective, the same cannot be said of older women 'at risk' whose BMD or fracture status is not known.[33] Research appears to confirm this fact whereby screening using fracture risk assessments, which include BMD, significantly reduces the risk of fracture and mortality, unlike fracture risk assessment without BMD.[34]

Taken together, these findings suggest a three-stage process is likely to be most effective either for screening or testing older men and women deemed to be at risk:

1 Use of an algorithm to identify those most in need of a DXA test

2 Measurement of BMD as per best practice guide, ideally hip and spine with a DXA or alternative test depending on availability

3 Fracture risk assessment uses a clinical algorithm that includes patients' BMD.

Conclusion

Osteoporosis and the associated fragility fractures are a global public health problem. A fragility fracture of the central skeleton or long bones of the arms or legs is diagnostic of osteoporosis. All such patients should be assessed and treated for osteoporosis and managed for fractures, pain, and rehabilitation.

Screening and diagnosis among populations without fractures is most effectively accomplished using a three-step process that includes DXA testing and fracture risk assessment. Correct use of the right algorithm and application of diagnostic and at-risk criteria will reduce the harms and waste associated with over-testing and over-treatment and maximise value and the quality of care for those most likely to benefit.

We have the tools to do this effectively today for both primary and secondary prevention, but considerable gaps remain between standards of recommended practice and their implementation in daily practice. Quantity is not quality, and cost is not value; in a world where quality and value matter, anything less is unacceptable.

Key learning points

- Osteoporosis, defined by compromised bone strength, is one of the most prevalent non-communicable diseases in the world today. The clinical consequence of this disease is skeletal failure, resulting in fragility fractures.
- A clinical diagnosis of osteoporosis can be made in the setting of a fragility fracture of the central skeleton and long bones of the limbs.
- Among populations without fractures, an assessment of bone density is usually required to make a diagnosis using a growing variety of imaging techniques. Diagnostic criteria are available for postmenopausal women, which can also be applied to men aged 50 years and older using clinical densitometry.
- Screening older men and women for osteoporosis is clinically and cost-effective since effective treatments are available for those at risk. Clarity around screening, diagnosis and risk assessment is needed.
- Several algorithms are available to address better ways to decide who should be screened by DXA testing, while more complex algorithms can estimate fracture risk. Appropriate use of the correct tool can help maximise the benefit of screening and early diagnosis, and minimise the cost and harms associated with over-testing.

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Osteoporosis: therapeutic management

A range of therapies is available for managing osteoporosis in postmenopausal women and men. Here, we consider these, their efficacies and tolerabilities, patient and drug selection and some of the challenges relating to long-term management of this condition

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Osteoporosis is often underdiagnosed, and thus not treated, often even after a fragility fracture has led the patient to the emergency department. A multidisciplinary, co-ordinator-based fracture liaison service is recommended by the National Osteoporosis Guideline Group (NOGG) in the UK to identify women and men with fragility fractures and to help with timely assessment of fracture and fall risk. For secondary fracture prevention programmes, collaboration between primary care clinicians, secondary care physicians, orthopaedic surgeons, radiologists and pharmacists, and between medical and non-medical disciplines involved in fracture liaison services is required.[1]

Tailored information about drug treatment should be offered to patients along with medication reviews to support adherence. Alternative therapies should be considered in cases of adverse events or where patients find adherence challenging.[1]

Pharmacotherapy and other approaches to treatment

Currently, available osteoporosis treatments are anti-resorptive (inhibiting the osteoclasts), bone-forming (stimulating the osteoblasts) or dual-acting (simultaneously stimulating the osteoblasts and inhibiting the osteoclasts).[2]

Anti-resorptive treatments include bisphosphonates, receptor activators of nuclear factor κB ligand (RANKL) antibodies and selective oestrogen receptor modulators (SERMs) that either cause osteoclast apoptosis (bisphosphonates) or inhibit osteoclast recruitment (RANKL antibodies and SERMs).[2]

Table 1 summarises some of the pharmacological and non-drug treatment options for osteoporosis.[1–3]

Clinical evidence of therapeutic choices: a snapshot

Different drugs and several options can be used in the treatment of osteoporosis based on the patient profile.

Bisphosphonates

Bisphosphonates have shown a 40–50% reduction in the risk of radiographic vertebral fractures at three to five years compared with placebo and a 20–30% reduction in non-vertebral and hip fractures.[4]

RANKL

Women between the ages of 60 and 90 years who had a bone mineral density T score of less than -2.5, but not less than -4.0 at the lumbar spine or total hip treated with denosumab 60 mg every six months for three years had a relative decrease in the risk of new radiographic vertebral fracture of 68% compared with placebo. There was a 40% relative reduction in the risk of hip fracture compared with placebo.[5]

The relative risk of any clinical fracture was reduced by 30% with denosumab treatment compared with placebo. After 36 months of treatment, participants who received denosumab saw a relative increase in bone mineral density of 9.2% (95% CI, 8.2–10.1) at the lumbar spine and 6.0% (95% CI, 5.2–6.7) at the total hip, as compared with those randomised to receive placebo.[5] After ten years of denosumab treatment, bone mineral density at the lumbar spine, total hip and femoral neck increased by 21.7%, 9.2% and 9%, respectively.[6]

In a study of 242 men with osteoporosis aged 31–84 years, significant increases in bone mineral density were seen following a year of treatment with denosumab compared with placebo, as follows: 4.8% at lumbar spine; 2.0% at total hip; 2.2% at femoral neck; 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all $p<0.05$). Denosumab increased lumbar spine bone mineral density from baseline in 94.7% of men at one year. Significant increases in bone mineral density at the lumbar spine, total hip, femoral neck and hip trochanter were observed by six months ($p<0.0001$).[7]

SERMs

The MORE trial investigated the effects of raloxifene. The drug reduced bone turnover and increased bone mass, but to a lesser degree than bisphosphonates and denosumab.[2] Treatment with raloxifene for three years resulted in a 30% reduction in the incidence of vertebral fractures but no significant decrease in non-vertebral or hip fractures; the risk of breast cancer was also reduced by more than 60%.[2]

Bone formation and hormonal therapies

Data from the Women's Health Initiative (WHI) trial demonstrated that hormone replacement therapy in 16,608 postmenopausal healthy women aged 50–79 years reduced the risk of osteoporotic fractures of the spine by 35%; of the hip by 33%; and of the wrist/lower arm by 29%. Long-term data from the trial showed no evidence for increased fracture risk after stopping hormone therapy.[4]

Treatment with teriparatide increases bone mineral density. The bone mineral density increases were more significant at the lumbar spine, predominantly trabecular bone, than at the hip sites. Teriparatide 20 µg daily reduced the risk of vertebral and non-vertebral fractures by 65% and 53%, respectively, compared with placebo after a median treatment duration of 21 months.[2]

TABLE 1

Treatment options for osteoporosis[1-3]

Drug class	Mode of action	Examples
Anti-resorptive drugs		
Bisphosphonates	Impede bone loss by inhibiting the activity of osteoclasts	Alendronate, risedronate, ibandronate, zoledronic acid
Selective oestrogen receptor modulators (SERMs)	Mimic oestrogen's bone-protective effects in postmenopausal women	Raloxifene
Bone resorption inhibitors	Inhibit bone resorption by osteoclasts and can also help reduce pain from spinal fractures	Calcitonin (salmon), strontium ranelate
Hormone replacement therapy (HRT)	Provides oestrogen to help maintain bone density in postmenopausal women	Oestrogen (often combined with progesterone)
Nuclear factor κ-B ligand (RANKL) inhibitors	Inhibit the formation, function and survival of osteoclasts	Denosumab
Bone forming drugs		
Hormone analogues	Stimulate new bone formation by mimicking the effects of parathyroid hormone	Teriparatide, abaloparatide, oestrogen
Dual action		
Sclerostin inhibitors	A newer class of drugs that increase bone formation and reduces bone resorption	Romosozumab
Non-drug approaches		
Dietary modifications (including vitamin supplementation)	Ensuring adequate intake of nutrients essential for bone health	Increased intake of calcium-rich foods (e.g., dairy products, leafy greens), vitamin D through sunlight or diet
Exercise	Regular weight-bearing and muscle-strengthening exercises that help maintain bone density	Walking, jogging, resistance training, yoga, Tai Chi
Lifestyle changes	Modifications that reduce bone loss and lower the risk of fractures	Quitting smoking, reducing alcohol intake, fall prevention strategies
Physical therapy	Exercises and techniques to improve balance, strength, and posture, reducing the risk of falls	Balance exercises, stretching routines, posture training
Fall prevention	Strategies to prevent falls, which are a major cause of fractures in people with osteoporosis	Home safety evaluations, use of assistive devices (e.g., canes, walkers), wearing proper footwear

Dual therapies

Romosozumab acts to both stimulate bone formation while also inhibiting bone resorption. In the FRActure study in postmenopausal woMen with ostEoporosis (FRAME) study, romosozumab increased bone mineral density at the spine by 13.3% and at the total hip by 6.8% after 12 months.[2]

In the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) study, the risk of vertebral fractures, non-vertebral fractures and hip fractures was reduced by 48%, 19% and 38%, respectively, after 24 months in women treated with romosozumab followed by alendronate compared with those receiving alendronate alone for 24 months.[2]

Treatment selection and initiation

When deciding on a drug treatment for people with osteoporosis, clinicians should consider fracture risk assessment, patient suitability and preference, the latest clinical evidence and cost-effectiveness.[1,3]

Antiresorptive therapy, such as oral bisphosphonates, is recommended by NOGG as first-line treatment for most people at risk of a fragility fracture. Alternative options include denosumab, hormone replacement therapy, raloxifene or strontium ranelate.[1] Patients are usually treated for three to five years with bisphosphonates, with another five years' treatment considered for those at high risk of fracture. Treatment for people over the age of 60 should be based on an individual risk–benefit analysis.[4] →

Hormone replacement therapy should be limited to younger postmenopausal women (aged 60 years or under) who have a low baseline risk for malignant or thrombotic events.[1] In December 2023, European regulatory authorities advised that hormone replacement therapy should not be used as a first-line treatment for osteoporosis prevention as the risks outweigh the benefits. The British Menopause Society notes that 'the view was robustly challenged, but despite a subsequent wealth of further evidence, the regulatory authorities have not revised their position'.[3] Hence, the recommendation for hormone replacement therapy to be offered to postmenopausal women aged under 60 years.[3]

NOGG says anabolic treatments such as teriparatide or romosozumab can be considered as a first-line option for postmenopausal women and men aged 50 years and older at very high fracture risk, particularly for those with vertebral fractures. The drugs can be offered as second-line options to those who cannot tolerate bisphosphonates.[1]

Long-term management with antiresorptive therapies: the challenges

The optimal duration of antiresorptive treatment for osteoporosis has not been determined. There are few data on the long-term efficacy, that is, more than ten years of treatment, or about the safety of combinations.[3] However, treatment with denosumab for up to ten years is associated with a favourable benefit–risk ratio regarding the fractures prevented compared with the incidence of adverse events. As osteoporosis is a chronic condition for most patients, long-term treatment and monitoring are needed.

Although there are currently only data for ten years of treatment with denosumab that does not mean that there should be an absolute limit on the duration of treatment with the drug. Indeed, the length of treatment will vary depending on factors such as starting bone mineral density, patient age, bisphosphonate tolerance, risk of falls, comorbidities and how long each patient takes to reach their target treatment goal.[6]

Situations in which treatment with denosumab may be discontinued include:[6]

- Patients who continue to be free of fractures and have a low fracture risk
- Patients who have a fracture, low or declining bone mineral density levels despite treatment with denosumab
- Patients who cannot tolerate denosumab treatment or experience severe adverse effects such as osteonecrosis of the jaw.

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There is some suggestion that an increased risk of vertebral fracture occurs after stopping treatment with denosumab. Most of the fractures happen within a year of stopping the drug. A post hoc analysis of the FREEDOM trial and its extension study found that the vertebral fracture rate increased from 1.2 per 100 participant-years (95% CI 0.9–1.6 per 100 participant-years) to 7.1 per 100 participant-years (95% CI, 5.2 to 9.0 per 100 participant-years).[5]

The rates of vertebral fracture after stopping denosumab were similar to those before and after stopping placebo.[5]

Vertebral fractures were seen in 34 out of 56 participants (61%) after denosumab was stopped, compared with 12 out of 31 participants (39%) in the placebo group. That equates to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively.[5] Interestingly, although bone loss was seen at all skeletal sites after denosumab treatment was stopped, there was no excess risk of other osteoporotic fractures.[8]

If denosumab treatment does need to stop, there is some evidence that follow-on therapy with an alternative drug may mitigate the loss of bone mineral density that might result.[8]

Some guidelines recommend that the need to continue treatment with denosumab for osteoporosis should be re-evaluated after five to ten years. Treatment with denosumab or other therapies for osteoporosis should continue for women who remain at high risk of fracture.[9]

Long-term treatment with denosumab may be associated with hypocalcaemia. The adverse event is rare, and most cases are mild and asymptomatic. Rates of hypocalcaemia among postmenopausal women with osteoporosis treated with denosumab have been reported in the range of 0.05–1.7% in randomised controlled trials.[10]

In a real-world study of 790 women with osteoporosis, 7.2% had serum calcium <8.5 mg/dL, and 1% had serum calcium <8 mg/dL. Nevertheless, it is a significant adverse effect of the drug. Monitoring serum calcium, vitamin D, magnesium and phosphate is important to prevent hypocalcaemia associated with denosumab treatment. Monitoring kidney function is also vital as chronic kidney disease increases the risk of hypocalcaemia occurring.[10]

Sequential treatment

Most patients with osteoporosis need to be treated for prolonged periods. Efficacy data and tolerability limit the use of currently available pharmacological treatments so sequential therapy is needed.[11]

Optimal treatment sequencing has not yet been developed, and patients who would benefit most from this approach have not been identified. There are no published data to help clinicians decide when to switch therapy: most changes are prompted by lack of efficacy or poor tolerability of current treatment.

For patients at lower risk of fracture starting with an antiresorptive drug seems reasonable, with bone-forming or dual-acting treatment as first-line therapy in cases of higher fracture risk.[11]

There is no definitive answer as to whether bisphosphonate treatment following a bone-forming or dual-acting drug can stopped, at least temporarily, but it may be logical to take the same approach as is used for bisphosphonate monotherapy to decide whether a drug holiday might be appropriate.

In treatment-naïve postmenopausal women with osteoporosis, starting with a bone-forming or dual-acting medication followed by an antiresorptive agent produces the most significant increase in bone mass. Starting treatment with a bisphosphonate may reduce the effectiveness of subsequent bone-forming or dual-acting therapies somewhat, although the strategy can be beneficial.[11]

It is advisable to avoid changing from denosumab to teriparatide (and possibly abaloparatide) because it can trigger accelerated bone remodelling and rapid bone loss.

Conclusion

A range of drug treatment options is available for the management of osteoporosis. Guidelines help clinicians decide which treatments might be most suitable for individual patients. Some specific points relating to tolerability and side effects must be considered when treating people with osteoporosis.

The optimal duration of antiresorptive treatment for osteoporosis has not been determined. Healthcare professionals should periodically reevaluate the need to continue therapies based on the benefits and potential risks for each individual, particularly after five to ten years of use.

Key learning points

- Osteoporosis is often unnoticed until it is too late. Collaboration between primary care clinicians, secondary care physicians, orthopaedic surgeons, radiologists, and pharmacists and between medical and non-medical disciplines involved in fracture liaison services is needed for secondary fracture prevention programmes
- When deciding on a drug treatment, fracture risk assessment, patient suitability and preference, the latest clinical evidence and cost-effectiveness should be taken into consideration.
- NOGG recommends antiresorptive therapy such as an oral bisphosphonate as first-line treatment for most people at risk of a fragility fracture
- Bisphosphonates have shown a 40%–50% reduction in the risk of radiographic vertebral fractures at three to five years compared with placebo and a 20%–30% reduction in the risk of nonvertebral and hip fractures
- The optimal duration of antiresorptive treatment for osteoporosis has not been determined. The need to continue treatments should be re-evaluated after five to ten years of use.

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Conclusion

The burden of osteoporosis is significant, not only in terms of the impact on the health and quality of life of those who have the disease, particularly as a result of osteoporotic fractures, but also upon the resources of health services.

Indeed, even minor fractures, such as rib fractures, can be associated with a notable increase in mortality, even in patients without comorbidities. The direct cost of incident fractures in Europe was calculated at €24.6 billion in 2010 and €36.3 billion in 2019, with long-term disability costs thought to be €10.7 billion in 2019, rising to €19 billion in 2019. Hip fractures had the most significant impact, accounting for 54% of the direct costs associated with the disease.

With an ageing population, that burden is set to grow: according to the International Osteoporosis Foundation, around one in ten (approximately 200 million) women aged 60 years worldwide are affected by osteoporosis. That proportion rises to 20% of women aged 70 and two-thirds of women aged 90.

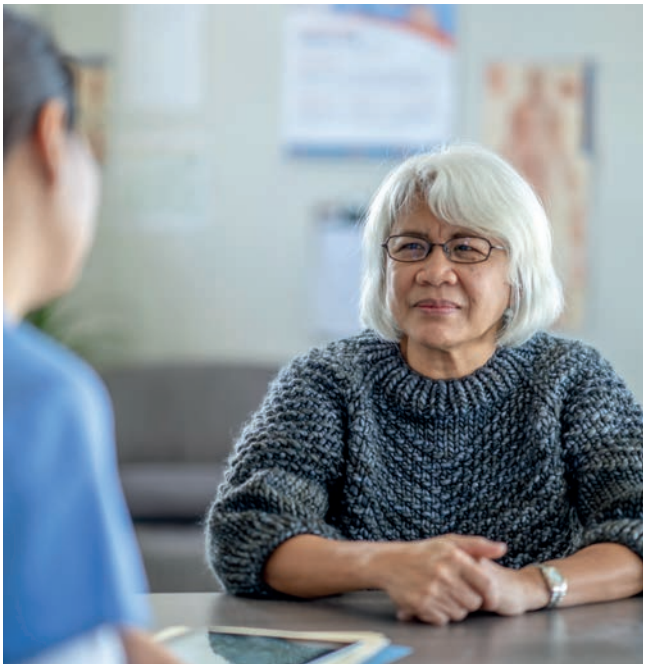
Risk factors for developing osteoporosis are understood, and some are modifiable, such as smoking, weight (low and high BMI are risk factors for low bone mass and fractures, respectively), diet, and exercise levels. Strategies to mitigate the effect of modifiable risk factors form a cornerstone of managing the disease. Pharmacotherapy to prevent fractures is available for people at high risk.

Screening and diagnostic techniques have evolved considerably, so it is now possible to detect patients at risk and grade their disease severity in those diagnosed with osteoporosis. These developments help healthcare professionals tailor treatment to individual circumstances to optimise outcomes.

It is essential to choose the appropriate age for screening. For example, the number of women aged 50 years and older who need to be screened to prevent one hip or one vertebral fracture is almost tenfold higher than when screening starts at age 65. The addition of another risk factor, such as body weight, could substantially reduce that number. This concept needs serious consideration because overdiagnosis in younger, healthier people could be as problematic as underdiagnosis among older, at-risk populations.

It should also be remembered that previous fractures are a significant risk factor for subsequent fractures, signalling an existing osteoporotic condition. It is crucial to look for and account for previous fractures to prevent future events.

When choosing which therapeutic approach to adopt for each individual, it is important to consider fracture risk assessment, patient suitability and preference, the latest clinical evidence and cost-effectiveness. Treatment is needed long term, but the optimal length of treatment has not yet been determined – data on efficacy beyond ten years and the safety of combinations are currently lacking. However, that does not preclude treatment for periods longer than ten years, provided the need to continue is re-evaluated periodically, particularly regarding the benefits and risks for the individual receiving treatment. Indeed, the length of treatment will vary depending on factors such as starting bone mineral density, patient age, bisphosphonate tolerance, risk of falls, comorbidities and how long each patient takes to reach their target treatment goal.



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While long-term tolerability and efficacy data for pharmacotherapy are currently lacking, treatment sequencing may offer a helpful strategy for managing over long periods. Although, again, more published evidence needs to support clinicians in this approach, some pointers in data do exist to provide a logical approach.

Our understanding and ability to detect, diagnose and treat osteoporosis have progressed, but challenges remain, particularly in optimising treatment and improving detection and prevention strategies. We hope this handbook will encourage you to continue to be curious about a disease that significantly impacts large numbers of individuals and strive to do all you can in your day-to-day clinical practice to improve the quality of life for these patients.

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