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Biosimilars in Osteoporosis Treatment: Focus on Denosumab

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Article Highlights

1. Despite the availability of effective treatments, there is a significant treatment gap in management of osteoporosis due to delayed diagnosis, undertreatment, and poor adherence
2. Biosimilars such as biosimilar denosumab can make treatment more affordable and accessible, offering effective yet less costly versions of biologic therapies
3. A patient-focused approach where doctors, nurses, and other healthcare workers work together is important for management of osteoporosis
4. Healthcare providers and nurses play a vital role in educating patients and involving them in decision-making, thus promoting adherence to treatment
5. Effective dental health management in osteoporosis requires collaboration between healthcare providers and dentists, along with patient education to reduce the risk of osteonecrosis of the jaw

Abstract

Introduction: Osteoporosis is a significant public health issue due to its associated morbidity, mortality, and economic burden. Despite available effective treatments, a treatment gap persists, characterized by delayed diagnosis, undertreatment, and poor adherence. Biosimilars, such as biosimilars for denosumab, offer an opportunity to improve treatment accessibility and affordability for osteoporosis and cancer-related bone loss.

Areas covered: This review explores the current treatment challenges in osteoporosis, the potential of denosumab biosimilars in improving access and outcomes, and the necessity of a multidisciplinary, patient-centered approach.

Expert opinion: The emergence of biosimilars for denosumab offers an opportunity to enhance accessibility and affordability of osteoporosis treatment, as biosimilars provide effective and economic versions of reference biologic therapies. A multidisciplinary approach is vital in managing osteoporosis, central to which is the patient, whose preferences, values, and lifestyle must guide the treatment plan. Healthcare providers play a crucial role in educating patients, promoting adherence to prescribed treatments, and involving patients in their own care to improve health outcomes.

Keywords: Biosimilar, bone loss, denosumab, multidisciplinary, osteoporosis, patient education, undertreatment

1 Introduction

Osteoporosis – defined by low bone mass, deterioration of bone tissue structure, and disruption of bone microarchitecture that heightens the risk of fractures – presents an ongoing public health challenge with considerable associated morbidity, mortality, and economic burden [1]. Affecting millions of people worldwide, with prevalence increasing alongside the aging population, osteoporosis is particularly common among postmenopausal women, men over the age of 50, individuals on long-term glucocorticoid therapy, and patients undergoing antihormone treatment for breast or prostate cancer [2]. Despite the availability of effective treatment options, a substantial proportion of patients receive inadequate therapy and experience poor outcomes. This treatment gap results from delayed diagnosis and significant undertreatment, often due to economic barriers, limited access to healthcare, misinformation regarding the risk of rare skeletal adverse effects of osteoporosis therapy, and insufficient patient education and awareness among healthcare professionals (HCPs), which leaves many patients vulnerable to fractures and associated complications [1,3,4].

The emergence of biosimilars in the treatment landscape for osteoporosis has created an opportunity to reduce this gap. Biosimilars, having the indistinguishable protein structure, and the same pharmacokinetic properties, efficacy and safety of their reference biologic medicines, typically provide effective versions of approved treatments at a reduced cost [5,6]. Nevertheless, while economic factors are important for access to treatment, other potential barriers include lack of patient and HCP awareness of the disease and therapeutic options, lack of understanding of the risk–benefit profile of treatment and misinformation about the risk of rare adverse effects, inadequate screening for fracture risk, and low rates of treatment adherence, which must be addressed to ensure that eligible patients can benefit from advancements in osteoporosis care [7–9].

Effective management of osteoporosis requires a coordinated approach that involves HCPs from various disciplines [10,11]. Heterogeneity of treatment pathways between healthcare settings can make it difficult to determine the best targets for educational initiatives. Ensuring that HCPs are well-informed about the latest developments, including the use of biosimilars, is crucial for optimizing patient outcomes.

In this review, we aim to reduce the awareness gap and set the stage for the expected impact of biosimilar denosumab on management of osteoporosis. We outline the current treatment

landscape and complexities of osteoporosis care, and discuss opportunities and challenges associated with the use of biosimilars, focusing on denosumab. We explore the implications of a multidisciplinary approach and patient-centered care for patients with osteoporosis and identify educational needs among both HCPs and patients.

2 Undertreatment in osteoporosis

2.1 Burden of disease

Osteoporosis has a reported estimated global prevalence of 18.3%, affecting one in three women and one in five men over the age of 50 years worldwide [2,12]. As the global population ages, the prevalence of age-related diseases such as osteoporosis is expected to rise. The burden of osteoporosis is multifaceted, encompassing clinical, economic, and social dimensions. Clinically, osteoporosis leads to an increased risk of bone fractures, which are associated with substantial morbidity and mortality [4,13]. In the US, the annual incidence of bone fractures is projected to increase by 68% to reach 3.2 million by 2040, compared to 1.9 million from 2018 [14]. Economically, osteoporosis-related fractures impose a significant financial burden on healthcare systems due to the costs of medical care, rehabilitation, and long-term disability. Including direct and indirect costs, the annual costs of fragility fractures in France, Germany, Italy, Spain, Sweden, and the United Kingdom are expected to increase by a quarter between 2017 and 2030, from €37.5 billion to €47.4 billion [13,15]. Socially, osteoporosis can lead to decreased mobility, loss of independence, and a reduced quality of life for individuals affected along with an increased financial burden for patients and the healthcare sector [16,17].

2.2 Overview of the management of osteoporosis

The ultimate goal of the management of osteoporosis is to improve bone health and reduce fracture risk. Alongside lifestyle modifications, pharmacologic options include antiresorptive therapies such as bisphosphonates, RANKL (receptor activator of nuclear factor-kappa B ligand) inhibitor (denosumab), selective estrogen receptor modulator (raloxifene), menopausal hormone therapy, parathyroid hormone analogues (teriparatide, abaloparatide), and a sclerostin inhibitor (romosozumab) (**Fig. 1**) [18].

Osteoporosis can be caused by antihormone therapies used in the treatment of prostate and breast cancer, as these medicines often result in decreased levels of hormones that are critical for maintaining bone density. In men with prostate cancer, androgen deprivation therapy (ADT) lowers testosterone and estrogen levels. Similarly, in postmenopausal women, treatment for breast cancer with aromatase inhibitors reduces estrogen levels. These hormonal shifts disrupt bone metabolism in both groups, resulting in bone fragility and a higher fracture risk [19].

Antiresorptive therapies can reduce fractures by 20–70% [20]. The ASBMR/BHOF (American Society for Bone and Mineral Research/ Bone Health and Osteoporosis Foundation) Task Force recommends tailoring treatment targets to each patient's unique risk profile, considering factors such as the specific indication for initiating treatment, prior fracture history (including timing, location, number, and severity), and bone mineral density (BMD) levels at key sites including the hip, femoral neck, and lumbar spine [21]. By utilizing measurable benchmarks, such as BMD, fracture incidence, and biochemical markers of bone turnover, clinicians can effectively apply a 'treat-to-target' approach, focusing on outcomes, monitoring, and reassessment in the management of osteoporosis [18,21].

2.3 The osteoporosis treatment gap

Despite significant progress in understanding the pathogenesis and treatment of osteoporosis, growing evidence shows that many patients who need pharmacologic treatment are either not being prescribed the appropriate medications or are not adhering to their treatment regimens [22]. Drivers for undertreatment include delays in diagnosis and risk assessment, poor treatment adherence, lack of medical education, and variation in healthcare policies [1,23].

2.3.1: Delays in diagnosis and risk assessment

Recommended priorities in screening and diagnosis

The Endocrine Society along with the European Society of Endocrinology emphasizes the heightened risk of subsequent fractures in patients who have already experienced a fracture. Recognizing this risk, the management of osteoporosis should begin with assessing the likelihood of future fractures using country-specific tools for informed decision-making [24].

For those at low or moderate risk, treatment should be guided by country-specific guidelines, as fracture risks, treatment options, and associated costs can vary significantly across different

populations. For those identified as being at high or very high risk, initiation of treatment with approved osteoporosis medications is a priority to help prevent further fractures. In postmenopausal women, and men aged more than 50 years, with low BMD and high fracture risk who are undergoing osteoporosis treatment, it is recommended to monitor BMD through dual-energy X-ray absorptiometry (DXA) scans of the spine and hip every 1 to 3 years to assess response to therapy [24,25].

Screening needs

Fracture as a warning signal of further fracture risk can be overlooked if mistakenly attributed to the normal aging process [14]. There is a lack of follow-up of vertebral fractures detected by radiography, despite their presence being associated with increased subsequent fracture risk [14]. Fracture prevention strategies are most effective when individuals at risk are identified; however, identification of patients with high risk of fracture can vary according to region-specific screening policies [9,26]. These fractures are best identified by the Fracture Liaison Service (FLS) [18,26]. While BMD is an important factor, incorporating additional risk factors alongside bone densitometry has been shown to improve the accuracy of fracture risk prediction [8]. A meta-analysis of three randomized studies – the ROSE (Risk-Stratified Osteoporosis Strategy Evaluation) study [27], the SCOOP (Screening in the Community to Reduce Fractures in Older Women) study [28], and the SOS (SALT Osteoporosis Study) study [26] – in the older population with high fracture probability found that screening with fracture risk assessment and bone densitometry, followed by anti-osteoporosis medication in primary care, significantly reduced osteoporotic fractures compared with usual care. Specifically, the risk of osteoporotic fractures (hazard ratio [HR]: 0.95), major osteoporotic fractures (HR: 0.91), and hip fractures (HR: 0.80) were lowered with no significant all-fracture reduction [9,26].

For patients receiving antihormonal therapy for cancer, seven international societies published a joint position paper to define risk factors for fragility fractures, screening strategies and optimal timing, dosing, and duration of therapy for bone loss [29]. Data from clinical trials show that antiresorptive treatment with denosumab and bisphosphonates reduces the risk of bone recurrence and significantly reduces breast cancer mortality. Since osteoporosis is typically asymptomatic until a fracture occurs, risk stratification to identify patients with early breast cancer or non-metastatic prostate cancer, selecting appropriate therapy, and closely monitoring

those at risk of bone loss, are crucial steps to reduce the incidence, burden, mortality, morbidity, and healthcare costs associated with the disease [29–31].

2.3.2 Treatment adherence and patient engagement

Treatment adherence, persistence, and duration substantially influence outcomes in the management of osteoporosis [18,32,33]. It is estimated that 25–30% of individuals with osteoporosis do not initiate their prescribed medication, and over 50% do not adhere to the treatment regimen beyond the first year [18]. Patients with suboptimal adherence and persistence experience a 30–50% higher incidence of fractures compared with those who follow the prescribed regimen, along with increased morbidity, mortality, and healthcare costs [34]. A common way to identify patients who are not adhering to medical treatment is to monitor bone turnover markers. The IOF (International Osteoporosis Foundation) and ECTS (European Calcified Tissue Society) have proposed the measurement of procollagen type I N-propeptide (PINP) or C-terminal telopeptide (CTX) before and 3 months after starting osteoporosis treatments, such as bisphosphonates, as the preferred way to identify nonadherence [33]. Compared with intravenous or oral bisphosphonates, 2-year persistence was found to be 1.5–2 times higher, and risk of discontinuation significantly lower ($P < 0.0001$) with denosumab in a retrospective analysis of women with first time prescription for osteoporosis in Germany [35]. Significant factors contributing to treatment nonadherence include the cost of high-efficacy medications such as denosumab and teriparatide; common side effects such as acute phase reaction with zoledronate or gastrointestinal disturbance with oral bisphosphonates; fear and overestimation of well-documented side effects such as atypical femur fractures and osteonecrosis of the jaw (ONJ); and a lack of awareness about support programs; for example, Own the Bone, and FLSs [18,34]. A meta-analysis found that patients receiving care through an FLS program, compared with those receiving usual care or those in the control arm, had higher rates of BMD testing (48.0% vs 23.5%), treatment initiation (38.0% vs 17.2%), and better adherence (57.0% vs 34.1%) [36].

Adherence with oral bisphosphonates has been reported to range from 28–85% over 1 year, and decreases further with each passing year [37]. Poor adherence is associated with an increased risk of fracture [37]. When adherence to denosumab was assessed in an electronic health record-based study, more than 20% of injections were administered with a delay of more

than 1 month. Patients with delays exhibited smaller increases in BMD at the lumbar spine and total hip [38].

As age is a significant risk factor, osteoporosis is best managed with ongoing therapy and monitoring, given that it has no cure. Bisphosphonate therapy is often discontinued after 3 to 5 years in a drug holiday to lower the risk of atypical femur fracture [18]. Discontinuing any pharmacologic treatment can lead to a decline in BMD and increase the risk of fracture returning to baseline levels or worsening further, but this is less of a problem with bisphosphonates as their effect persists for some time after stopping. Switching treatments at different stages of the disease – i.e. due to a nonresponse to treatment, adverse events, or the limited approved duration of use for anabolic agents – can help in maintaining any experienced therapeutic benefits [18,20,39]. The AACE/ACE (American Association of Clinical Endocrinologists/American College of Endocrinology and Endocrine Society) 2020 guidelines, as well as the recommendation of the ECTS, recommend against a drug holiday with denosumab, as stopping treatment has been associated with a decline in BMD after 1 year and an increase in bone turnover markers after 3 to 6 months [40–42]. We discuss this issue further in the section on denosumab, section 3.2.

2.3.3 Healthcare policies

The intricacies of market access, healthcare provision, insurance, and reimbursement are beyond the scope of this article, but restricted reimbursement has been reported as a significant obstacle to accessibility and long-term uptake of medicines for osteoporosis [13]. Tong et al. (2022) investigated the accessibility and affordability of monoclonal antibody and Fc-fusion protein biologic medicines in the Asia Pacific (APAC) region between 2010 and 2020, finding that by 2020, middle-income APAC countries (China, India, Indonesia, Malaysia, Philippines, Thailand, and Vietnam) had fewer biologic medicines available compared with high-income countries in the region (Australia, Hong Kong, Japan, Korea, New Zealand, Singapore, and Taiwan). Additionally, the availability of biologics in APAC countries was lower than in benchmark countries such as Canada, the United Kingdom, and the United States. The analysis also revealed significant disparities in the consumption of biologic medicines, with emerging and developing APAC nations using fewer biologics overall compared with both high-income APAC countries and benchmark nations [23].

3 The advent of biosimilars in bone health

3.1 Introduction to biosimilars

Biosimilars are biologic medicines described as ‘equivalent not identical’ to an already approved biologic ‘reference’ medicine; key features are detailed in **Table 1**. This distinction arises because biologics (both reference and biosimilar) are made from living organisms and therefore have natural variability that cannot be perfectly replicated, for example, differences in post-translational modifications [5,6].

Benefits associated with biosimilars include increased access to biologic therapies, reduced healthcare costs, and the fostering of competition and innovation within the pharmaceutical industry. The introduction of biosimilars into the pharmaceutical market at the point of patent expiry of the reference medicine can lead to substantial savings for patients, healthcare systems, and payers, while maintaining high standards of safety and efficacy [43]. It has been reported that US healthcare systems have saved 36 billion USD through the use of biosimilars since the approval in 2015 of the first biosimilar, filgrastim, for patients with cancer receiving chemotherapy and radiation therapy [47,48].

3.2 Biosimilars in bone health

The use of biosimilars in the management of osteoporosis can improve treatment access and affordability for patients, providing a cost-effective alternative to reference biologic therapies, thereby helping to address the growing demand for pharmacologic osteoporosis treatment. The first approved biosimilar for osteoporosis treatment (approved in 2017) was for a biosimilar to the reference medicine teriparatide, the active pharmaceutical ingredient of which is the 1–34 fragment of endogenous human parathyroid hormone, which has demonstrated benefits in bone density and fracture prevention through the stimulation of bone formation. Teriparatide biosimilars, generics, and the reference medicine are approved for the treatment of osteoporosis in patients at high risk of fractures; however, they are not approved for treating bone loss associated with antihormone therapy in breast and prostate cancer [49–51].

Unlike hormone-based teriparatide, denosumab, a biologic medicine first approved in 2010 [52,53], is a monoclonal antibody that exerts its effect by targeting and inhibiting RANKL, a critical protein involved in the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. By blocking RANKL, denosumab reduces osteoclast activity,

thereby decreasing bone resorption and promoting an increase in BMD. This mechanism helps to enhance bone strength and reduce fracture risk [49]. Thus, in the key FREEDOM study of denosumab in postmenopausal osteoporosis, the relative increases in lumbar spine and total hip BMD were 9.2% and 6.0%, respectively; the reduction in the risk of vertebral and hip fractures was 68% and 40%, respectively [55]. In the open-label extension of FREEDOM (10 years of treatment), there were increases in lumbar spine and total hip BMD of 21.7% and 9.2%, respectively [56].

Alongside its indications for osteoporosis (postmenopausal and glucocorticoid-induced) in patients with high fracture risk, denosumab is also used to increase bone mass in patients at high risk of fracture who are receiving hormone therapy for breast or prostate cancer [52,53]. Denosumab is administered subcutaneously, 60 mg every 6 months. The adverse reactions associated with denosumab include severe hypocalcemia and mineral metabolism changes, serious infections, and dermatologic adverse reactions [52,53]. However, most of these adverse reactions are rare and denosumab is usually well tolerated [52,53]. Upon discontinuation, the beneficial skeletal effects can reverse rapidly as denosumab circulates in the bloodstream, binds to secreted RANKL in the extracellular fluid, and is cleared through the reticuloendothelial system, with a half-life of around 26 days. This rebound in the BMD effect of denosumab is termed the 'overshoot phenomenon', and is due to an increase in osteoclast activity, which can lead to rapid bone loss and subsequent multiple vertebral fractures as bone turnover markers not only return to baseline levels but often exceed them [57–59]. Thus, to maintain the benefits achieved with denosumab therapy, it is recommended by the AACE/ACE, The Endocrine Society, and ECTS that patients transition to bisphosphonates, preferably zoledronic acid (intravenous), once discontinuation of denosumab is confirmed [40,42,60]. A clinical trial showed some attenuation of the increase in CTX with zoledronic acid 5 mg given 6, 9, or 12 months after the last dose of denosumab; there was still some loss of BMD over two years [61]. In an observational study, the bone loss was less if patients were given oral bisphosphonates or zoledronic acid in the three years following denosumab cessation [62]. Although most research has been done with zoledronic acid, there is some clinical trial evidence that alendronate may prevent any overshoot, but this has only been shown in one study (Denosumab Adherence Preference Satisfaction [DAPS] study) after just 1 year of denosumab treatment [63]; we await further trials on this topic. Also, we do not know whether the effect of bisphosphonates is related to the duration of denosumab use, and we await further trials on this topic, too.

The ECTS has identified key risk factors for patients at increased risk of multiple vertebral fractures following discontinuation of denosumab therapy, including the duration of treatment (exceeding 3 years) and a strong BMD response to denosumab, and prior history of vertebral fractures [42]. Initiating a potent bisphosphonate such as zoledronic acid upon stopping denosumab and monitoring the treatment's effectiveness using bone turnover markers is recommended. If bone turnover markers are unavailable, administering a second dose of zoledronic acid after an additional 6 months is suggested [42].

Using denosumab in sequence with anabolic agents such as teriparatide, abaloparatide, and romosozumab has been shown to maximize benefits for patients at very high risk of fractures [64]. The IOF-ESCEO (International Osteoporosis Foundation–European Society for Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases) recommends using denosumab after teriparatide for patients with a very high fracture risk due to osteoporosis, excluding those undergoing cancer treatments [8]. It is not recommended to follow denosumab with teriparatide as any anabolic effect is attenuated [39]. The FRAME (FRActure study in postmenopausal woMen with ostEoporosis) study found that starting osteoporosis treatment with romosozumab significantly improves bone density and reduces fracture risk, with continued benefits when transitioning to denosumab [58].

The first denosumab biosimilar, by Sandoz, was approved internationally in 2024, marking a significant milestone in the advancement of osteoporosis care. Its indications match those of the reference medicine [66,67]. As of 2025, there are currently three denosumab biosimilars that have been approved both by the FDA and EMA at the time of writing (Jubbonti®, Sandoz; Ospomyv™, Samsung; Stoboclo®, Celltrion) and an additional biosimilar (Conexxence®, Fresenius Kabi) approved by the FDA only [68–70]. Sandoz denosumab was compared with reference denosumab in postmenopausal women with osteoporosis, and the lumbar spine BMD increases were similar (both 5.0% at 12 months) [71]. Samsung denosumab was compared to reference denosumab in postmenopausal women with osteoporosis, and the lumbar spine BMD increases were similar (5.6% and 5.3%, respectively, at 12 months) [72]. In postmenopausal women with osteoporosis, Celltrion denosumab and reference denosumab produced similar increases in lumbar spine BMD at 12 months (5.0% vs. 5.1%) [73]. As compared to reference denosumab, there were similar changes in CTX, similar rates of hypocalcemia and anti-drug antibodies, and switching from reference to biosimilar denosumab resulted in similar changes in BMD [73–75]

As denosumab therapy becomes more economically accessible, and consequently available to patients for whom it had not previously been considered, it will be important for HCPs to be aware of the recommendations on management of the overshoot phenomenon. Understanding that the benefits of denosumab treatment can be maintained after discontinuation by transitioning patients to intravenous bisphosphonates may ensure that prescribers have confidence to initiate denosumab treatment when clinically warranted.

3.3 Awareness of biosimilars among HCPs

In a systematic review exploring the factors affecting uptake of biosimilars, it was observed that HCPs have limited understanding of biosimilars, and that they are more comfortable in prescribing biosimilars to patients who are naïve to biologics than to those switching [7]. This limited understanding may stem from confusion between biosimilars and generic medicines. Biosimilars are equivalent with minor differences to the reference biologic medicine and require extensive testing (including clinical trials) prior to approval to demonstrate similarity in safety and efficacy, while generics are chemically identical to the original small-molecule drug and only need to prove bioequivalence to the reference drug. Biosimilars are produced through complex biologic processes and may exhibit slight variations in structure and function, unlike generics which are exact replicas of their reference drugs [6,76]. These results signify the importance of providing HCPs with evidence to increase their confidence in biosimilars, and to widen the options available to patients.

Long-term data from the use of biosimilars, including real-world evidence on their safety and effectiveness from analysis of post-marketing experience, have a role in helping HCPs to gain confidence in prescribing biosimilars. Such studies might also aid in clarifying unresolved or partially resolved issues, such as authorized indications, switching, and the immunogenicity of biosimilars, and promote use of biosimilars in routine practice [77,78]. A review summarizing the real-world safety experience for eight marketed biosimilars (adalimumab, epoetin alfa, etanercept, filgrastim, infliximab, pegfilgrastim, rituximab, and somatropin) concluded that the overall benefit–risk profile of each remains favorable and is consistent with the respective reference biologic [66].

4 Multidisciplinary and patient-centered care in osteoporosis

Effective management of osteoporosis involves the collaboration of multiple HCPs (**Fig. 2**). Each of these specialists brings unique expertise and perspectives, contributing to a comprehensive care plan tailored to the individual needs of the patient [10,11,79]. Effective sharing of critical patient information between primary care physicians and specialists is crucial for supporting consistent care, which can lead to better patient outcomes, and increased satisfaction for both providers and patients. However, this communication is often inadequate, as demonstrated by a 2020 survey of 7,183 General Practitioners from 34 countries, which identified issues such as limited nursing support and difficulties in specialist collaboration, with significant variation across different countries [68].

4.1 Management of osteoporosis in patients with cancer

Cancer therapies can exacerbate bone loss at a rate more than seven-fold higher than that of normal aging [69]. Early cancer diagnosis and a rapidly changing treatment landscape in oncology have led to improved survival outcomes in patients with cancer, resulting in an increased likelihood of patients experiencing long-term side effects from cancer treatments, such as bone loss and fractures [29]. Managing osteoporosis in patients undergoing treatment for cancer is therefore important and necessitates a multidisciplinary approach (**Fig. 2**).

As mentioned, cancer therapies such as chemotherapy and radiotherapy along with hormonal therapy (gonadotropin-releasing hormone agonists, aromatase inhibitors, ADT), have been shown to contribute to bone loss. Radiotherapy-induced bone loss primarily occurs due to direct damage to the bone, whereas chemotherapy-induced bone damage alongside glucocorticoids given to avoid side effects, may result from either direct targeting of the bone or indirect systemic effects. Hormonal therapy for cancer targets estrogens and androgens, both of which play a part in maintaining bone mass, and therefore disruption of these hormones can result in bone loss [81,82].

Recent guidelines from an international expert panel of clinical oncologists and specialists in metabolic bone disease recommend that clinicians use risk assessment tools to estimate osteoporosis risks in patients treated for cancer, with BMD testing every 2 years [29,83]. Furthermore, the ASCO (American Society of Clinical Oncology) Clinical Practice Guideline for osteoporosis in survivors of adult cancers with non-metastatic disease recommends a range of non-pharmacologic interventions. These recommendations include monitoring calcium and

vitamin D intake, promoting a tailored exercise regimen (including balance, flexibility, endurance, and strength training), and encouraging cessation of smoking and limiting alcohol consumption [69].

Seven interdisciplinary cancer and bone societies (IOF, CABS [Cancer and Bone Society], ECTS, IEG [International Expert Group for aromatase inhibitor-associated bone loss], ESCEO, IMS [International Menopause Society], and SIOG [International Society for Geriatric Oncology]) have concluded that administering denosumab 60 mg or zoledronic acid 4 mg every 6 months during adjuvant aromatase inhibitor therapy is recommended to prevent aromatase inhibitor-associated bone loss in postmenopausal women. Zoledronic acid is recommended when the focus is on minimizing disease recurrence, while denosumab is preferred when fracture risk is the primary concern [29]. In patients on ADT, treatment with bisphosphonates or denosumab is recommended [71]. The rebound phenomenon has been observed after stopping denosumab given for aromatase inhibitor-induced osteoporosis [84].

4.2 Management of dental health in patients with osteoporosis

Current evidence demonstrates an association between antiresorptive therapies such as bisphosphonates and denosumab, and an increased incidence of ONJ [85,86]. ONJ is a condition where the jawbone becomes exposed and fails to heal for at least 8 weeks in patients taking antiresorptive therapies [54]. Notably, the prevalence of ONJ is markedly higher in oncology patients receiving high-dose regimens (<5%) compared with those treated for osteoporosis with low-dose protocols (<0.05%) [85–87].

Effective management of dental health in patients with osteoporosis requires a collaboration between dentists and other HCPs . Proactive communication between dentists and other specialists about upcoming dental procedures is important for making collaborative decisions on dosing and other preventive measures [88]. Sharing patient histories, treatment plans, and monitoring protocols between HCPs can help minimize the potential oral health implications of osteoporosis [86,88]. Invasive dental procedures should be considered carefully in patients taking antiresorptive medications. The American Dental Association (ADA), for example, recommends a thorough review of the patient's medical history and assessment of the risk of ONJ during dental examinations to ensure appropriate dental care by the dentist. It is crucial to address conditions that can lead to infection, such as caries, dental plaque, periodontitis, and apical periodontitis, with conservative treatments to avoid further complications [86,88,89]. It is

important to involve and educate patients about dental risk management. The ADA recommends an oral health program consisting of maintenance of good oral hygiene and regular dental check-ups, which are vital for monitoring and minimizing the risk of ONJ [86]. Though the risk of ONJ is lower than the risk of multiple osteoporotic fractures [54], dentists should remain vigilant in assessing oral health in individuals with osteoporosis. Implementing screening protocols in dental settings could enhance the early identification of at-risk patients [88,90]

4.3 Patient-centered care in osteoporosis

Central to any multidisciplinary treatment approach is the patient, whose preferences, values, and lifestyle must guide the management plan. Taking the time to understand patient choices and addressing any fears or misconceptions during the treatment selection process can improve treatment adherence, and lead to better outcomes for patients [18]. Thus, patients should be encouraged to share their questions and concerns about treatments, dosing schedules (daily, weekly, monthly, every 6 months, or yearly), benefits, and potential side effects when reviewing medication options with them [18,91]. Educating patients about osteoporosis includes advising the patient and any caregivers about osteoporosis and its consequences, discussion of lifestyle issues, the modification of risk factors, and importantly, compliance with their medication [18,92].

Furthermore, ensuring a clearer understanding of the benefits of biosimilars for patients is important for treatment success and to minimize the risk of nocebo effects. A patient education program that provides information on how biosimilars work, how they differ from small molecule generic medicines, and how the regulatory approval process ensures safety and efficacy of biosimilars, will help improve patient awareness of the benefits of biosimilars [77].

Specialist nurses play a pivotal role in patient education, breaking down complex medical information into understandable terms, providing personalized advice, and building trusting relationships with patients [94,95]. Specialist nurses educate patients on healthy lifestyles, including nutrition, exercise, and smoking cessation, while promoting adherence to prescribed medications and supplements. Nurses can also contribute to fall-reduction programs, assist with early osteoporosis detection, and provide ongoing support to minimize recurrent fractures in patients with a history of fragility fractures [96,97]. In a single center study in Taiwan, it was observed that patients who received education from nurses were more than five times more likely to choose out-of-pocket anti-osteoporotic therapy (mostly denosumab) than those who did

not receive such education [82]. Physiotherapists also have an important role in managing osteoporosis through exercise prescription, therapeutic modalities, specific techniques, and patient education. Appropriate treatment goals can be set after a comprehensive evaluation of signs, symptoms, osteoporosis risk factors, and functional status, with the aim of preserving bone mass, minimizing fall risk, enhancing posture, alleviating pain, and improving mobility and physical function [99,100].

In a systematic review of the effectiveness of patient education for patients with osteoporosis, published in 2022, 13 studies met the inclusion criteria and had covered at least two aspects [85]. Six studies examined improvements in physical function, and all found a positive effect of education; two of three reported improvements in psychological wellbeing, and only one of five studies reported a benefit for physical comfort and disability. Effects on quality of life, adherence, persistence, and knowledge of osteoporosis were inconclusive. The impact of patient education in improving the management of osteoporosis is an area that requires further research [85].

5 Conclusion

Osteoporosis remains a substantial public health issue, affecting the quality of life of millions of individuals globally, and requiring comprehensive, effective, and affordable treatments. Denosumab has a central role in the management of osteoporosis in patients at high fracture risk, providing substantial long-term benefits including sustained improvements in BMD, and with potential for treatment sequencing with anabolic agents. Furthermore, denosumab shows strong clinical efficacy in managing cancer-related bone loss in patients with breast and prostate cancer. The introduction of denosumab biosimilars presents a promising advancement in the management of osteoporosis. By offering effective versions of expensive biologic therapies at a lower cost, biosimilars may increase treatment accessibility and help to address the treatment gap that currently exists. Economic accessibility alone, however, is not sufficient. HCPs must be well-informed about the use of biosimilars to confidently prescribe them, and patients need to be educated about the benefits and potential of these treatments. The collaborative effort of all stakeholders – patients, clinicians, and HCPs – is imperative to advance the management of osteoporosis, allowing patients at a high risk of bone fractures to receive the necessary treatment to minimize bone loss, and reduce the likelihood of future fractures. By leveraging the

potential of denosumab biosimilars and fostering a multidisciplinary, patient-centered approach, we can achieve better health outcomes and ensure optimal bone health for all.

6 Expert Opinion

Despite the availability of effective treatments, there is a significant treatment gap in management of osteoporosis due to delayed diagnosis and undertreatment [1,3,4]. The development of biosimilars, like biosimilar denosumab, have the potential to impact real-world outcomes in treating patients with osteoporosis. These biosimilars provide effective and economic versions of expensive biologic therapies, thus addressing significant economic barriers and ensuring that more patients at high risk of fractures receive necessary treatment, along with improving treatment adherence [46,50]. Denosumab, a monoclonal antibody targeting RANKL, has improved osteoporosis treatment by reducing osteoclast activity, thereby decreasing bone resorption and increasing BMD. This mechanism enhances bone strength and reduces fracture risk, thus making denosumab a crucial treatment option [49]. The multidisciplinary approach emphasized in the review highlights the importance of patient-centered care, which can play an important role in better adherence and effectiveness [18]. However, the realistic implementation of these advances into clinical practice is contingent upon overcoming several barriers. One major obstacle is the lack of awareness and education among HCPs and patients regarding the benefits and safety of biosimilars.

Key areas for improvement include enhancing patient and HCP awareness through comprehensive education and training programs, improving screening and diagnosis protocols, and increasing treatment adherence [1]. Current screening methods may not adequately identify patients at high risk of fractures, leading to delayed diagnosis and treatment. Implementing more accurate and comprehensive screening tools can help in early detection and timely intervention, thereby reducing the incidence of fractures and associated complications [9,26]. Technological advancements, such as improved bone densitometry techniques with the integration of additional risk factors into fracture risk prediction models, can help overcome current limitations [8]. Addressing the economic barriers through policy changes and financial support programs is crucial for ensuring that patients can access these treatments.

Many HCPs are hesitant to prescribe biosimilars due to concerns about their efficacy and potential side effects [7]. Extensive testing to demonstrate biosimilarity is necessary to ensure the safety and efficacy of biosimilars. The regulatory authorities are actively working to further

streamline the approval process for biosimilars, aiming at facilitating quicker market access while ensuring patient safety and maintaining therapeutic efficacy. The FDA recently proposed removal of the requirement for switching studies between a biosimilar and its reference product, provided that a robust, comprehensive analysis of available data demonstrating equivalence in terms of safety, efficacy, and immunogenicity is provided [5,6,43,45]. Methodological improvements in clinical trials and real-world evidence studies can provide robust data to support the efficacy and safety of biosimilar treatments.

Specific to denosumab, exploring sequential therapies with anabolic agents, such as teriparatide and romosozumab, may maximize the benefits and provide more effective solutions for patients at very high risk of fractures [64]. In addition, increasing use of personalized medicine, early integration of nutrition and lifestyle interventions, and advanced imaging techniques can offer significant advancements in the diagnosis and management of osteoporosis [18,39], thereby improving patient outcomes.

Proactive communication between a patient's dentist and HCPs is important for managing dental issues in those receiving osteoporosis treatments such as denosumab to reduce risk for ONJ. Good oral hygiene along with regular dental check-ups are also advised to minimize risk [86,88]. Specialist nurses play a critical role in managing osteoporosis by educating patients in healthy lifestyles, promoting adherence to medical regimens, and providing ongoing support, which can lead to improved outcomes and patient satisfaction [94]. Physiotherapists similarly contribute by prescribing tailored exercise programs and providing education to enhance physical function and bone health [99,100]. Adherence to prescribed treatment is crucial in managing osteoporosis, and regular physical activity supports treatment outcomes [18].

Evolution in the field of osteoporosis management through increased use of biosimilars, improved patient education, and the use of personalized treatment approaches will ultimately lead to better patient outcomes, reduced healthcare costs, and a standardized approach to managing osteoporosis. Overall, the future of osteoporosis management looks promising, with biosimilars playing a central role in advancing patient care and improving health outcomes.

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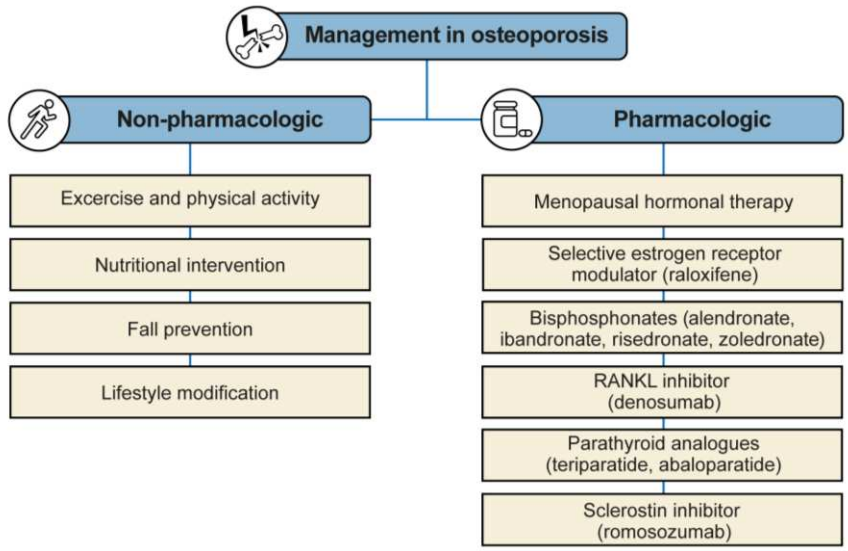
Figures and tables

Fig. 1 Management approaches in osteoporosis



RANKL, receptor activator of nuclear factor-kappa B ligand

Fig. 2 Multidisciplinary management of osteoporosis

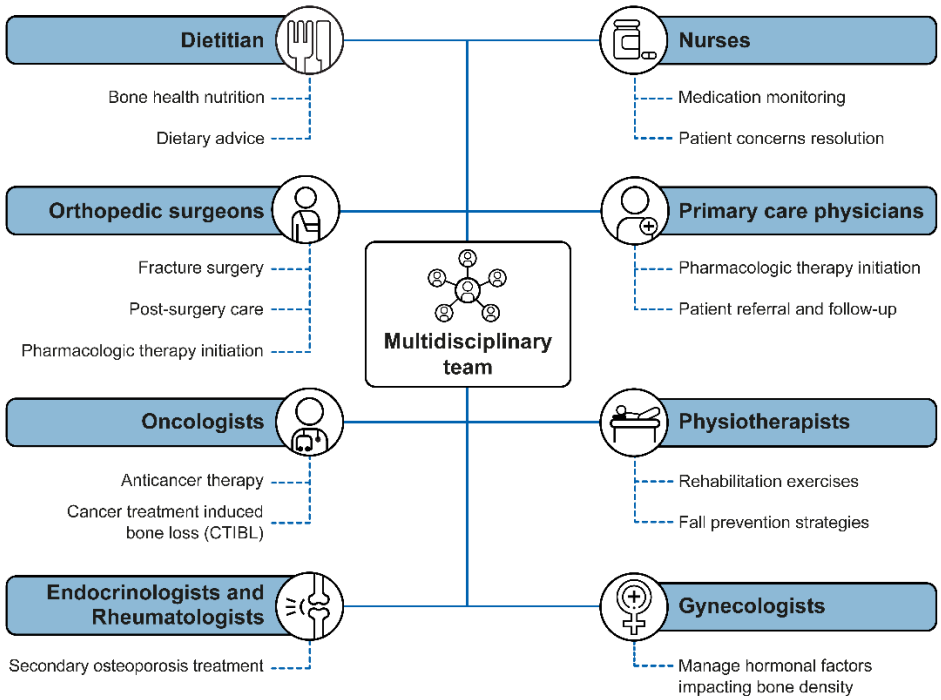


Table 1 Key features of biosimilars [5,6,43–45]

Approval pathway	Both stringent, requiring demonstration that there are no clinically meaningful differences in safety, purity, and potency compared with the reference medicine, and abbreviated, as unlike new medicine development the biosimilar pathway aims to confirm comparability to the reference medicine rather than establish efficacy
Authorization of indications	Approved for one indication of the reference medicine; can be approved for other indications without the need for direct clinical trials, based on the totality of evidence supporting its biosimilarity
Interchangeable	Biosimilars are approved as interchangeable by the EMA and Heads of Medicines Agency; the US FDA currently requires additional switching studies for biosimilars seeking interchangeable status, but it has recently proposed removing this requirement if adequate comparative data are provided

EMA, European Medicines Agency; FDA, Food and Drug Administration

Figure legend

Fig. 1 Management approaches in osteoporosis

RANKL, receptor activator of nuclear factor-kappa B ligand

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