



# Osteoporosis Management: Gaps in Patients' Care and Treatment

# 21

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## Introduction

Osteoporosis is a major public health threat in the United States and around the globe. As of 2010, 10.2 million adults have osteoporosis and another 43.4 million have low bone mass, a figure expected to rise nearly 30% by the year 2030 (Fig. 21.1). Osteoporosis is the major cause of fragility fractures, which are from low trauma not likely to occur in healthy bone, in the population age 50 and above. Taking the American population as an example, as osteoporosis prevalence increases parallel with aging, the number of fragility fractures may increase from two million in 2005 to three million in 2025 [1, 2]. Patients who sustain fragility fractures will, most likely, experience the morbidity/comorbidity consequent upon fracturing. Furthermore, fragility fractures cause substantial pain and severe disability, often leading to a reduced quality of life. In addition, hip and vertebral fractures are associated with decreased life expectancy. Patients who have had any one fracture have an increased risk of subsequent fractures. The US Preventive Services Task Force recommends osteoporosis screening and treatment after a first fracture due to increased risk of future fractures, including a 20-fold greater risk for a clinically serious hip or spine

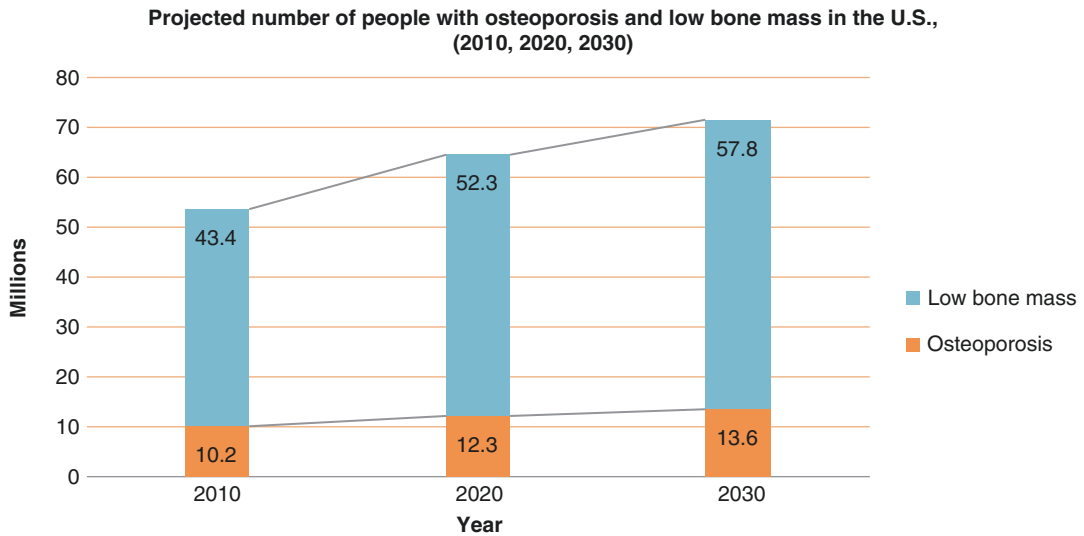
fracture [3, 4]. The National Osteoporosis Foundation considers all postmenopausal women and men older than 50 years with prior hip or vertebral fracture as candidates for osteoporosis treatment [5].

Fortunately, osteoporosis is a preventable disease that can be diagnosed and managed before any fracture occurs. Previous studies suggest that sex, age, race, education level, insurance type, baseline calcium use, fracture site, prior osteoporosis diagnosis, previous fracture, chronic comorbidities, and history of cigarette smoking are predictors of the use of osteoporosis medication for secondary prevention of further fractures [6–11]. In patients who have already experienced a fracture, the appropriate use of available therapies can effectively decrease the risk of future fractures by up to 50%. Yet osteoporosis is underdiagnosed and undertreated worldwide, and secondary fracture risk is poorly addressed in patients who have sustained a first fracture [12–21].

This chapter will start by discussing the need to treat in osteoporosis, followed by highlighting the gaps in osteoporotic patients' care as well as treatment. The chapter will expand to analyse and describe approaches to close these gaps and lastly and present the most recent guidelines for the management of osteoporosis.

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**Fig. 21.1** Projected number of people with osteoporosis and low bone mass in the United States (2010, 2020, 2030)

## Osteoporosis: The Need to Treat

Many guidelines for the assessment and treatment of osteoporosis recommend that intervention be considered in men and women who have sustained a fragility fracture [22]. Guidelines in North America [23, 24] specifically refer to a prior hip fracture, as well as spine fracture, as mandatory indication for treatment because of the marked effect of fractures at these sites on both morbidity and mortality. In addition, hip fractures have large economic consequences. For example, hip fractures account for 17% of all osteoporotic fractures in Europe but comprise 54% of the direct cost of fractures [22]. The need for treatment arises because of the increased risk of a second fracture [25], which is particularly acute in the immediate post-fracture period when fracture rates are substantially increased [26–28].

Despite a number of advances, particularly in the diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures, and the production of practice guidelines, many surveys indicate that a minority of men and women at high fracture risk actually receive treatment [29–35]. According to the 2008 Joint Commission Report, *Improving and Measuring Osteoporosis*

Management, only 20% of patients with low-impact fractures in the general population are ever tested or treated for osteoporosis or receive therapies to reduce the risk of future fracture within the year following the fracture [13, 36–39].

In another large observational cohort study, only 6.6% of hip fracture patients received calcium and vitamin D after surgery [12]. Paradoxically, the therapeutic care gap may be particularly wide in the elderly in whom the importance and impact of treatment is high; studies have shown that as few as 10% of older women with fragility fractures receive any osteoporosis therapy (oestrogens not considered) [40, 41]. Furthermore, treatment rates following a fracture are lower for those individuals who reside in long-term care [33]. This contrasts with the situation following myocardial infarction, for which condition a significant care gap has been overcome in the past 15 years: 75% of such individuals now receive beta blockers to help prevent recurrent myocardial infarction [42].

Osteoporosis is a silent disease that progresses without the evidence of symptoms until a fracture occurs. Fragility fractures are responsible for considerable pain and suffering, severe disability, reduced quality of life, and use of long-term care and rehabilitation resources [43]. The leading

cause of the loss of independence in men or women 70 years of age and older are fragility fractures due to falls at home [44]. Most patients do not regain their pre-fracture functionality or independence and many are permanently limited in mobility, ability to fulfil social roles, and performance of activities of daily living and self-care [45]. Psychological consequences have also been noted, such as loss of self-efficacy, depression, and anxiety [46].

The economic burden due to osteoporotic fractures is high and will escalate as the population ages. Overall, the medical cost of osteoporosis and related fractures is estimated to be \$20 billion per year. The annual cost in the United States of caring for osteoporotic-related fractures alone parallels or exceeds the annual cost for myocardial infarction, breast cancer, and/or cerebrovascular accidents [47]. Direct costs are predicted to escalate to \$25 billion by 2025 and \$50 billion by 2050 due to the increase in the incidence of osteoporotic fractures [48].

In the United States, two million osteoporotic fractures occur every year. One of two women and one of five men will sustain an osteoporotic fracture in their lifetime [49]. For women over 50 years, the lifetime risk of a fracture is higher than the combined risk of developing cervical, uterine or breast cancer, while men over 50 it is higher than risk of developing prostate cancer [50]. The incidence rates of fragility fracture due to osteoporosis at all skeletal sites increase with advancing age in both women and men, with those 85 years and older at highest risk [51].

Furthermore, an initial fragility fracture increases the absolute risk of sustaining future fractures for both men and women [52]. An individual who sustains a fracture is 86% more likely to sustain a fracture of another type [53]. For men, although their risk for an initial fracture is lower than that of women, once they sustain an initial fracture, their risk for additional fractures escalates to the same level of risk for subsequent fracture as women in their age group. For women, an initial fracture increases their risk for subsequent fracture as high as or higher than the initial fracture risk carried by women in the 10-year age group above theirs. Research has demonstrated

increased risk for future fracture applies to virtually all clinical fracture sites, is highest immediately after the initial event, and persists for up to 10 years [54].

Premature mortality associated with fracture, particularly following hip and vertebral fractures, is well documented [55, 56], and evidence of elevated mortality risk following other types of osteoporotic fractures is mounting [55]. Risk of death is most pronounced in the first three to 6 months after sustaining a fracture and the risk increases substantially with subsequent fractures [57]. The cumulative incidence of adverse outcomes following all low-trauma fractures leads to the death in 39% women and 51% men within 5 years and excess mortality related to fracture can extend up to 10 year. These mortality rates far exceed that expected for an age- and sex-matched population (24% in women and 27% in men) [58].

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## Osteoporosis: Gaps in Care

Osteoporosis is a preventable disease that physicians can diagnose and manage in the early stages of low bone mass. For reducing morbidity and mortality associated with osteoporosis-related fractures, it is imperative to recognize individuals at risk for osteoporosis. Yet, contrary to recommendations for universal screening and treatment, osteoporosis is vastly underdiagnosed and undertreated worldwide. Considering the reasons linked to such paradox, three gaps in patient care could be identified challenges facing healthcare professionals and policymakers responsible for providing care to populations in relation to bone health.

### Gap 1: Failure to Follow Guidelines for Screening for Osteoporosis

Based on the analysis of medical claims data collected from a large American cohort between 2008 and 2014, screening rates among privately insured women ages 50+ were persistently low. Only 26.5% women in the age group

65–79 and 12.8% women 80 years and older had measurement for their bone mass. Even lower utilization rates were seen among non-Hispanic black women and women of low socioeconomic status [59].

There is also evidence that physicians who do screen may not be following recommended diagnostic guidelines and may be making the treatment decisions based on incorrect assumptions. The analysis of 5 years of electronic health and radiological records at a regional health care system in United States revealed two-thirds of women receiving new medication prescriptions for osteoporosis therapy did not need treatment. In fact, one half of the women being treated may not have qualified for screening at all, because they were of younger age and had no risk factors for osteoporosis [60]. Another study found that family physicians order bone densitometry and try to manage osteoporosis appropriately but lack a rationale for testing [61]. Surveys on physicians' learning needs indicate the majority (66.8–83.2%) want to be informed about criteria for ordering and the interpretation of densitometry reports and T-scores and the frequency of testing [62, 63].

In conclusion, the first gap in the patients' care lies in the hands of the physicians who need information regarding who and when to test, guideline-based diagnostic criteria and indications for testing, and information on how to interpret tests.

## **Gap 2: Failure of Secondary Fracture Prevention**

Secondary fracture prevention is an obvious first step in the development of a systematic approach to prevention of all fragility fractures caused by osteoporosis. Early aggressive treatment intervention after a first low-trauma fracture, especially in those with low bone density, can reduce the risk of additional fractures and associated premature mortality. Since the 1980s, it has been reported that up to one half of hip fracture patients have already sustained a previous fracture [64–

67]. Meta-analyses have shown that individuals who have sustained a fracture are at approximately double the risk of sustaining subsequent fractures, as compared to their fracture-free peers [68, 69]. However, data show that the percentage of patients receiving a treatment for osteoporosis, even after sustaining a hip fracture, has declined in the United States from 41% in 2001 to 21% in 2011. These numbers demonstrate a low participation of physicians in their patients' secondary fracture prevention.

The effectiveness of the broad range of currently available osteoporosis treatments has been comprehensively reviewed [70]. Cochrane Collaboration systematic reviews have evaluated most of the anti-osteoporotic medications for secondary fracture prevention. The outcomes documented the effectiveness of the available osteoporosis treatments to reduce future fracture risk. Therefore, it is of great concern that a pervasive and persistent secondary prevention care gap is evident throughout the world. The International Osteoporosis Foundation (IOF) Capture the Fracture® program website provides an up-to-date bibliography of all PubMed cited secondary prevention audits and surveys, undertaken internationally, nationally, regionally, and locally [71].

In response to this widely documented care gap, models of care have been developed in many countries to ensure that fragility fracture patients receive secondary preventive care – which includes both osteoporosis management and intervention to prevent falls – in a consistent and reliable fashion. The most common models are referred to as orthogeriatrics services and fracture liaison services (FLS) [72].

In conclusion, physicians need information regarding the range of anti-osteoporotic agents available for treatment and how to select the appropriate one for each patient, drug safety profiles, dosing instructions, timing of initiation of medication, and how to treat patients at moderate risk for fracture. The implementation of services such as orthogeriatrics and fracture liaison service does help in secondary fracture prevention.

### Gap 3: Patient-Physician Communication Failure

This lack of patient awareness and action is coupled with a lack of healthcare professional (HCP) awareness and intervention. Multiple studies demonstrate that patients diagnosed to have osteoporosis tend to underestimate their risk of becoming osteoporotic and are less concerned about the consequences of osteoporosis than other diseases. Earlier studies assessing osteoporotic patients who have multiple FRAX risk factors, one-third did not believe they were at an increased risk for future fracture [73, 74]. Even when patients have had fragility fractures, more than half do not link their fractures with osteoporosis even when told they have the disease, nor do they appear to understand they are at increased risk for future fracture [75].

Patient education on low bone mass and osteoporosis is imperative for long-term management of osteoporosis and fracture prevention. Therefore, it is crucial for physicians to communicate to patients that a diagnosis of osteoporosis, increasing age, or a fragility fracture increases the risk of future fracture. However, surveys and focus groups indicate primary care physicians feel there are barriers to communicating with elderly patients about the complexity of osteoporosis risk and fracture prevention, which include time constraints, the complexity of their other health problems, and their reluctance to add new medications to long lists of prescribed therapies [61, 63].

In conclusion, better approaches to deliver the message such as informative video clips, adverts, or information leaflets to highlight the magnitude of the issue to the patients, educate and empower them to actively participate in shared decision-making, and support self-care and medication adherence as well as persistence. Physicians need training to enable them to provide clear physician-patient communication and patient education that can help patients understand their risk and agree to adhere to a management pathway.

### Osteoporosis: Mind the Treatment Gap

Despite the increasing number of effective drugs to treat osteoporosis, discouraging evidence suggests that there is a growing gap in treatment options. This has been evidenced by the finding that many patients who should receive pharmacological treatment are either not being offered these drugs or, when prescribed, not taking them [76]. This has also been reported in patients recovering from hip fracture, for whom there is universal agreement of the importance of pharmacological therapy [77]. Although many reasons exist for this gap in osteoporosis treatment, perhaps the two most important reasons are fear of rare side effects and concerns regarding long-term efficacy.

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### Fear of Rare Side Effects

In an article published earlier in the *New York Times* Gina Kolata [78], patient concerns with side effects, particularly atypical femur fractures, were highlighted as an important contributor to the lack of appropriate treatment for osteoporosis. Although these side effects have only been clearly associated with bisphosphonates, patient perceptions about these risks are extending to all osteoporosis drugs, which is particularly concerning because atypical femur fractures are extremely rare. So although the relative risk of atypical femur fractures in patients taking bisphosphonates is increased, the absolute risk ranges from 3.2 to 50 cases per 100,000 person-years [79]. When used in patients who are at high risk of fracture, these drugs are estimated to prevent 80–5000 fragility fractures for each atypical femur fracture possibly induced by treatment [80]. Several steps can be taken to address this problem [81], such as improved patient and doctor education regarding both the risk-benefit ratio of these drugs and the prodromal symptoms (e.g., groin or hip pain) of atypical femur fractures; potential use of dual x-ray energy absorptiometry to monitor patients on therapy specifically for

features of atypical femur fractures [82]; identification of high-risk patients using femur geometrical characteristics and other risk factors for atypical femur fractures [83]; and the development of pharmacogenomic markers identifying patients at increased risk of atypical femur fractures.

A second rare side effect of bisphosphonate use is osteonecrosis of the jaw, which was initially described in the setting of high-dose bisphosphonate use in patients with metastatic cancer. This side effect is extremely rare in patients treated at doses recommended for osteoporosis, with an estimated incidence of 0.001–0.01% [84]. Again, better education of patients, doctors, and dental practitioners, along with maintenance of good oral hygiene and dental health, are key to overcoming this barrier to treatment.

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### Concerns Regarding Long-Term Efficacy

As highlighted by a position statement from the FDA [85], data regarding the anti-fracture efficacy of bisphosphonates after 5 years of use is scarce and perhaps conflicting. This assessment, combined with the observation that the risk of the rare side effects of atypical femur fractures and osteonecrosis of the jaw increases with duration of therapy [79, 84], has led to legitimate concerns about the long-term (>5 years) treatment of patients with bisphosphonates or other anti-resorptive agents, such as denosumab. However, data from the Fracture Intervention Trial Long-term Extension (FLEX) [86] showed that postmenopausal women with low hip T scores (–2.0 to –2.5) who continued treatment with alendronate for 10 years had fewer clinical vertebral fractures than women receiving placebo after 5 years had. Similarly, in the HORIZON extension study of zoledronic acid [87], women with T scores less than –2.5 had fewer morphometric vertebral fractures after six annual infusions than women who received only 3 years of treatment had. On the basis of these studies, current recommendations are to treat patients who warrant

therapy with a bisphosphonate for 5 years and then reassess, basing subsequent treatment on the level of fracture risk and potentially considering a so-called drug holiday for a variable period of time, albeit in the absence of data showing the efficacy of this approach [88]. Long-term treatment (up to 10 years) with denosumab in an open-label extension of the FREEDOM trial has been shown to have a persistent benefit by reducing non-vertebral fractures [89].

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### Osteoporosis: Closing the Gaps

Osteoporosis is a preventable disease that physicians can diagnose and manage in the early stages of low bone mass. Recognition and management of individuals at risk for osteoporosis is imperative for reducing morbidity and mortality associated with osteoporosis-related fractures. This part of the chapter will provide a comprehensive overview of the state of osteoporosis care for individuals at high risk of suffering fragility fractures and how to close the gaps in both the patients' care and treatment. The different 'gaps' identified are listed in Table 21.1; to facilitate their discussion and approach to handling, they have been clustered into four major themes. Given current projections indicating that the burden of fragility fracture is heavy and expected to grow over the coming few decades, it is imperative that governments, key opinion leaders, and national patient societies work together now to ensure that epidemiological data are available to inform policy development. There is much to be done. Therefore, the task now is to ensure the dissemination and adoption of these best practice examples, adapted for local considerations, in order to tackle the current, and future, burden of fragility fractures worldwide.

### Closing Gap 1: Secondary Fracture Prevention

In 2012, the IOF issued a report on the World Osteoporosis Day devoted to the global Capture the Fracture® Campaign [64, 90]. Approximately

**Table 21.1** Gaps in care and treatment of patients diagnosed to have osteoporosis

Theme	Gaps in care and treatment
Case finding and management	Gap 1: Secondary fracture prevention Gap 2: Osteoporosis induced by medicines Gap 3: Diseases associated with osteoporosis Gap 4: Primary fracture prevention for individuals at high risk of fracture
Public awareness	Gap 5: The importance of staying on treatment Gap 6: Public awareness of osteoporosis and fracture risk Gap 7: Public awareness of benefits versus risks of osteoporosis treatment
Government and health system issues	Gap 8: Access and reimbursement for osteoporosis assessment and treatment Gap 9: Prioritization of fragility fracture prevention in national policy
Lack of data	Gap 10: The burden of osteoporosis in the developing world

half of the patients admitted with hip fracture suffered a prior fragility fracture in the months or few years before breaking their hip [64, 65, 67, 91], representing an obvious opportunity and, indeed, imperative for assessment and intervention to be carried out to prevent future fractures. The report also cited numerous audits undertaken across the world to establish what proportion of fracture patients received the osteoporosis care that they needed: in the absence of a systematic approach, less than a fifth received such care. Whilst some exciting progress has been made to close this care gap, many publications and initiatives since 2012 highlight that there is still a huge amount of work to be done throughout the world. This was reviewed in a dedicated publication by the international osteoporosis foundation [92]. Clinically effective models of care, namely, orthogeriatrics and fracture liaison services, have been developed in many countries to close the secondary prevention care gap in a highly cost-effective manner.

## Models of Care: Orthogeriatrics Services and Fracture Liaison Services

In response to the well-documented secondary fracture prevention care gap, innovators throughout the world have developed models of care designed to ensure that health systems respond to the first fracture to prevent second and subsequent fractures.

- *Orthogeriatrics services* (OGS): The need for effective orthopaedic–geriatric co-care of patients admitted to hospital with hip fractures is well recognised in professional guidance [93–95]. Such models of care focus on expediting surgery, ensuring optimal management of the acute phase through adherence to a care plan overseen by senior orthopaedic and geriatrician/internal medicine personnel, and delivery of secondary fracture prevention through osteoporosis management and falls prevention.
- *Fracture liaison services* (FLS): The fracture liaison service (FLS) model of care has also been adopted in many countries. The purpose of an FLS is to ensure that all patients aged 50 years or over, who present to urgent care services with a fragility fracture, undergo fracture risk assessment and receive treatment in accordance with prevailing national clinical guidelines for osteoporosis. The FLS also ensures that falls risk is addressed among older patients through referral to appropriate local falls prevention services.

These two service models are entirely complementary. As the adoption of orthogeriatrics services for hip fracture sufferers becomes more widespread, orthogeriatrics services are increasingly likely to deliver secondary preventive care for these patients. As hip fractures constitute approximately 20% of all clinically apparent fragility fractures, in health systems which have implemented orthogeriatrics services, FLS will provide secondary preventive care for the other 80% of fragility fracture sufferers who have experienced fractures of the wrist, humerus,

spine, pelvis, and other sites. This ‘division of labour’ is illustrated in the falls and fractures pyramid in Fig. 21.2, which was first presented in policy developed by the Department of Health for England in 2009 [96]. A similar approach has been advocated in Australia [97], Canada [98], New Zealand [99], and the United States [100, 101].

For the vital role of secondary fracture prevention, as well as both orthogeriatrics services and FLS as a reliable means to deliver this care to fracture patients, this has been addressed and featured in a growing number of clinical guidelines and government policies.

### Closing Gap 2: Medication-Induced Osteoporosis

Many widely used medicines have been associated with decreases in bone mineral density and/or increased fracture incidence, although these links have not been proven as causal in every case. A 2014 review described the potential pathogenesis of bone loss associated with all of these classes of medicines [102, 103]. Table 21.2 shows a list of these medications. This section will focus on three very commonly used agents: glucocorticoids for a range of conditions, androgen deprivation therapy for treatment of prostate cancer in men, and aromatase inhibitors for the

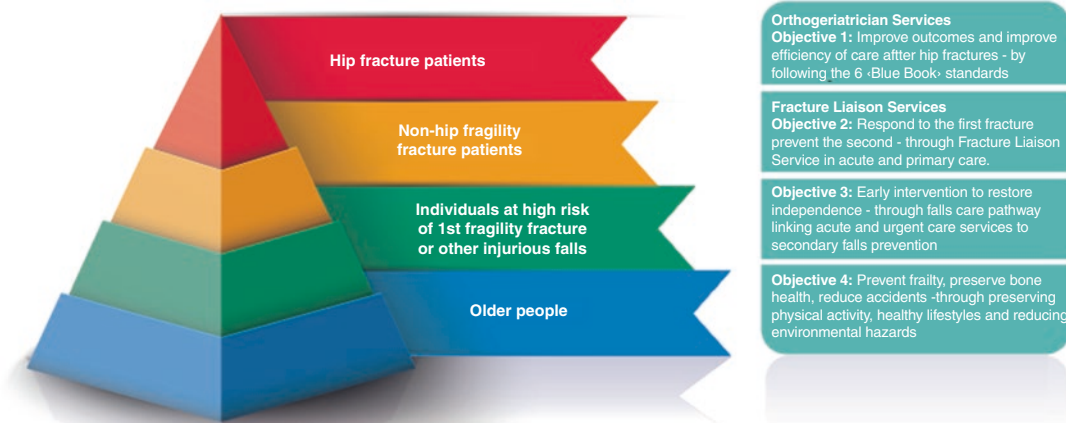
treatment of hormone receptor-positive breast cancer in women.

### Steroids-Induced Osteoporosis

Steroids are very commonly used to control inflammation in the setting of a broad range of conditions including autoimmune dermatological and respiratory diseases, as well as malignancies and organ transplants. Estimates suggest that 1 in 13 adults aged 18 years and over have been prescribed oral steroids at some stage of their life [103]. Up to 30–50% of patients receiving chronic glucocorticoid therapy experience clinically apparent fragility fractures and/or asymptomatic vertebral fractures, making steroid-induced osteoporosis the leading cause of secondary osteoporosis

**Table 21.2** Osteoporosis induced by medicines

Medications most commonly associated with osteoporosis
Glucocorticoids
Proton pump inhibitors
Selective serotonin reuptake inhibitors
Thiazolidinediones
Anticonvulsants
Medroxyprogesterone acetate
Hormone deprivation therapy
Calcineurin inhibitors
Chemotherapies
Anticoagulants



**Fig. 21.2** Orthogeriatrics services and fracture liaison services as components of a systematic approach. (Quoted from reference [96] under open access scheme)



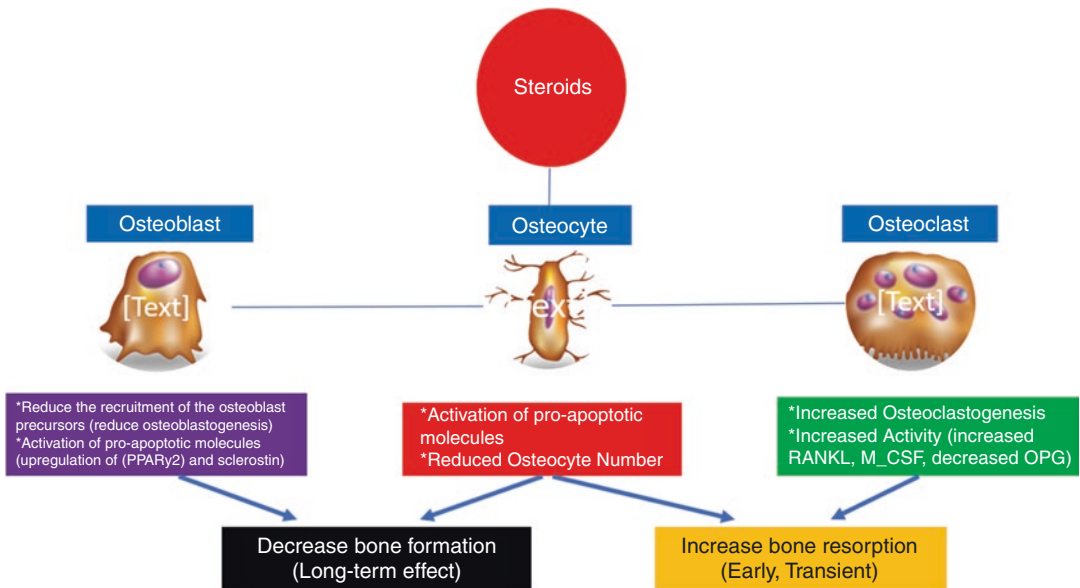
sis [104]. Meta-analysis has shown previous steroid use to be associated with a relative risk of 2 for any fracture at the age of 50 years and 1.7 at the age of 85 years [105]. For osteoporotic fracture, the range of relative risk is 2.6 and 1.7; and for hip fracture 4.4 and 2.5 for the same age groups.

Steroids have a direct impact on the bones as it affects both the function and numbers of the three major types of bone cells [106–110] (Fig. 21.3):

- Osteoclasts: Stimulation by steroids results in prolonged survival of osteoclasts, leading to excessive bone resorption, particularly in trabecular bone in the spine.
- Osteoblasts: By reducing the recruitment of the precursors to osteoblasts, the number of mature osteoblasts is reduced, resulting in decreased bone formation.
- Osteocytes: Osteocyte apoptosis (cell death) is triggered by steroids and may contribute to an increase in fracture risk prior to a reduction in bone mineral density (BMD).

Steroids' indirect effects on bone: Other mechanisms that may contribute to glucocorticoid-induced bone loss through indirect effects on bone include hypogonadism, reduced physical activity, increased renal and intestinal losses of calcium, and reduced production of growth hormone, insulin-like growth factor 1 (IGF1), and IGF1 binding protein (IGF-BP) [111]. In addition, the underlying diseases for which glucocorticoid therapy is administered are often associated with increased inflammation, which contributes to bone loss through increased production of pro-inflammatory, pro-resorptive cytokines. Whilst glucocorticoids suppress inflammation and hence should mitigate the adverse effects of inflammation, disease relapse despite therapy is associated with episodes of increased bone resorption. Finally, glucocorticoid excess has adverse effects on muscle mass and function, leading to myopathy and increased risk of falls [112, 113].

To close this gap, clinical guidelines for the prevention and treatment of glucocorticoid-induced



**Fig. 21.3** Direct effects of glucocorticoids on bone. PPAR $\gamma$ 2: Peroxisome proliferator-activated receptor gamma receptor 2 (favoring the differentiation of pluripotent precursor cells to adipocytes in preference to osteoblasts). Sclerostin: It binds to the co-receptors for frizzled, Lrp4 and Lrp5, resulting in the inhibition of Wnt signaling, leading to reduced differentiation of osteoblast precursors to mature osteoblasts and increased osteoblast and osteo-

cyte apoptosis. M-CSF macrophage colony stimulating factor, RANKL receptor activator of nuclear factor- $\kappa$ B ligand, OPG osteoprotegerin. (Increased M-CSF and RANKL and decreasing production of OPG by osteoblastic cells and osteocytes result in an increase in both the number and activity of osteoclasts. This effect diminishes with time, possibly as a result of the reduction in number of osteoblasts and osteocytes)

osteoporosis are already available in several countries. The European League Against Rheumatism (EULAR) [114] and a Joint Guideline Working Group of IOF and the European Calcified Tissue Society (ECTS) [115] have produced internationally relevant guidance. Whilst the detail of individual guidelines varies somewhat, the common theme is that individuals receiving chronic steroids therapy are at increased risk of fracture on account of taking steroids, and, in a significant proportion, the risk is great enough to warrant the offer of preventive treatment. An organized programme of care – GIOP (Glucocorticoid-Induced Osteoporosis Program) – has been implemented in the United States in order to improve preventive care for members [116]. The programme goals are to identify patients at risk of fracture, provide education, redesign and implement new pathways of care, and monitor outcomes.

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### Androgen Deprivation Therapy-Induced Osteoporosis

**Pathogenesis:** Androgen deprivation therapy (ADT), in the form of gonadotropin-releasing hormone agonists (GnRHs), limits the production of testosterone and estradiol, leading to chemical castration [102]. GnRHs elicit this effect by reducing the secretion of luteinizing hormone and follicle-stimulating hormone. This is a consequence of GnRHs binding to GnRH receptors in the pituitary gland and downregulating the gonadotropin producing cells.

The beneficial clinical effects of ADT in men with symptomatic metastatic prostate cancer are rapid and dramatic [117]. ADT is universally accepted as the first-line treatment of symptomatic metastatic prostate cancer [118]. Prostate cancer is the most common non-cutaneous malignancy in men, with 1 in 6 men being diagnosed during their lifetime [119]. Approximately half of men diagnosed with prostate cancer will receive ADT at some stage after diagnosis [120]. A meta-analysis of relevant studies reported that between 9% and 53% of survivors had osteoporosis [166]. A rapid decline in BMD is observed during the first year of ADT treatment [121]. A cohort study

based on medical claims data from Medicare beneficiaries in the United States compared fracture rates for men with non-metastatic prostate cancer who initiated GnRH agonist treatment against a comparison group who did not receive GnRH agonist treatment [122]. The men treated with GnRHs had statistically significantly higher rates of any clinical fracture (relative risk [RR]: 1.2), vertebral fractures (RR: 1.5), and hip/femur fractures (RR: 1.3). Longer duration of treatment also conferred greater fracture risk.

To close this gap, clinical guidelines relating to the prevention and treatment of ADT-induced osteoporosis have been published in several countries. Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in urology departments to establish what proportion of ADT treated patients have undergone osteoporosis assessment and received guideline-based care.

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### Aromatase Inhibitor-Induced Osteoporosis

**Pathogenesis:** Aromatase inhibitors (AIs) reduce oestrogen levels by the inhibition of the peripheral conversion of androgens to oestrogens. This results in lower oestrogen levels with a consequent increase in bone turnover and bone loss.

Aromatase inhibitor use and fracture incidence: Breast cancer is the most common neoplasm and primary cause of cancer-related mortality in women, affecting 1 in 8 women worldwide. Aromatase Inhibitors currently represent the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer [123]. The annual rate of bone loss observed for women taking Aromatase Inhibitors of around 2.5%. This figure is elevated compared to healthy postmenopausal women who lose about 1–2% per year [124].

The analysis of the Women's Health Initiative Observational Study compared fracture rates among breast cancer survivors with women with no history of breast cancer at baseline [125]. After adjustment for factors related to hormone levels, risk of falls, prior fracture history, medica-

tion use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was 15%. Studies comparing two commonly used aromatase inhibitors, anastrozole [126] and letrozole [127], with tamoxifen have reported significant increases in fracture risk for the aromatase inhibitor-treated patients. A comparative study of anastrozole with exemestane showed similar fracture rates [128]. A position paper from the European Society for Clinical and Economical Aspects of Osteoporosis (ESCEO) has comprehensively documented studies on the skeletal effects of aromatase inhibitors [124].

The care gap for aromatase inhibitor-induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and steroid-induced osteoporosis care gaps have been discussed. Clinical guidelines relating to the prevention and treatment of aromatase inhibitor-induced osteoporosis are available in several countries. Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in oncology departments to establish what proportion of aromatase inhibitor-treated patients have undergone osteoporosis assessment and received guideline-based care.

### **Closing Gap 3: Diseases Associated with Osteoporosis**

There are many health problems which can increase an individual's risk of developing osteoporosis and suffering fragility fractures [129]. These include a broad array of disorders: autoimmune, digestive and gastrointestinal, endocrine and hormonal, hematologic, neurological, mental illness, cancer, and AIDS/HIV. These include also malabsorption, anorexia nervosa, primary or secondary hypogonadism, dementia, and diabetes.

In many of these conditions, there is lack of specific guidelines for management of osteoporosis, whereas clinical guidelines relating to the prevention and treatment of associated osteoporosis is available in some countries for some of these conditions. Working Group comprised of clinical experts in the field of COPD and fracture prevention published a 5-step approach which includes

case finding, risk evaluation, differential diagnosis, therapy, and follow-up [130]. Clinical guidelines relating to the prevention and treatment of osteoporosis in celiac disease are available. Similarly, guidelines relating to the prevention and treatment of osteoporosis in inflammatory bowel disease (IBD) have been published [92].

The estimated number of people living with dementia in 2013 was estimated to be 44.4 million, a figure set to increase to 75.6 million and 135.5 million by 2030 and 2050, respectively. The largest increases in the projected number of dementia sufferers will be in East Asia and Sub-Saharan African regions. By 2050, the proportion living in what are currently low- and middle-income countries will increase to 71%, compared to 62% in 2013. In 2010, the global societal cost of dementia was US\$604 billion, representing 1% of global GDP [131], and 486,000 people died as a result of dementia worldwide [132].

A significant overlap exists between sufferers of dementia and older people at high risk of injurious falls and fractures; this is particular evident amongst patients presenting with hip fracture. A UK study published in 2009 found that during a 12-month period, 66% of participants with dementia had a fall compared with 36% of age-matched controls [133]. Furthermore, the incidence of falls in dementia was nine times higher than that observed among a control group. The incidence of hip fracture among patients with Alzheimer's disease has been reported to be almost three times higher than amongst cognitively healthy peers [134]. In a meta-analysis, the prevalence of dementia amongst older hip fracture patients was estimated to be 19% [135]. The prevalence of cognitive impairment was estimated at 42%. In 2007, the Scottish Hip Fracture Audit reported on the prevalence of dementia amongst hip fracture patients [136]. Over a quarter (28%) of patients had a documented past medical history of dementia, which the authors indicated was likely to be a significant underestimate of actual prevalence on account of the poor diagnosis rates for dementia documented at that time.

In 2011, a monograph on the subject of dementia, falls, and fractures summarised the current evidence [137]:

- Persons with dementia suffer more falls, more fractures, and higher post-fracture mortality than those without dementia, yet they are under-assessed for falls risk factors and are less likely to receive treatment for osteoporosis.
- Falls and fracture patients have a high prevalence of dementia and cognitive impairment, yet do not routinely receive cognitive assessment and, consequently, frequently miss an opportunity for a diagnosis of dementia to be made.

Subsequent studies from Canada [138], Finland [139], the United Kingdom [121], and the United States have added to the evidence that osteoporosis is infrequently diagnosed and treated in people living with dementia.

As the population of dementia sufferers is set to grow spectacularly in the coming decades, evidence-based guidelines for the management of osteoporosis – and falls risk – in dementia must be drafted and implemented as soon as possible.

#### **Closing Gap 4: Primary Fracture Prevention**

Whilst the prevention of secondary fractures remains a priority, in the long term, the ultimate goal would be the prevention of the first fracture. Advances in the fracture risk assessment during the last decade provide a platform for development of clinically effective and, crucially, cost-effective approaches for the identification of those individuals at high risk of a primary fracture. In order to ensure that a primary fracture prevention programme has the potential to be cost effective, consideration must be given to which first fragility fracture is to be prevented. Primary prevention of hip fracture is likely to be more cost-effective than primary prevention of wrist fracture, because hip fractures cost considerably more to manage than wrist fractures. In this regard, consideration must be given to what proportion of all hip fractures occur as an individual's first fragility fracture at any skeletal site [93].

Whilst definitive data are not available to give an accurate estimate of the primary hip fracture

incidence, the following illustration is consistent with the current evidence-base:

- Approximately 50% of hip fracture patients have suffered clinically apparent fragility fracture(s) prior to breaking their hip, which was usually a non-vertebral fracture [64, 65, 67, 91].
- Conservative interpretation of studies from Spain and Japan suggests that a further 10% [140] to 25% [141] of hip fracture patients may have suffered previous vertebral fractures – the majority of which are not recognised or diagnosed as such [142] – but have not suffered clinically apparent non-vertebral fractures.
- Therefore, 25–40% of hip fracture patients may have suffered the hip fracture as their first overt fragility fracture at any skeletal site.

This analysis highlights the challenge faced by efforts to proactively case-find the relatively small proportion of individuals who are likely to suffer a hip fracture as their first fragility fracture. It should also be noted that fragility fractures at sites other than the hip impose a significant burden on older people.

Vertebral fractures lead to many adverse consequences for sufferers, including [143]:

- Back pain, loss of height, deformity, immobility and increased number of hospital bed days [144, 145]
- Reduced quality of life resulting from the loss of self-esteem, distorted body image, and depression [146–149]
- A significant negative impact on activities of daily living [150, 151]

Studies from Australia [152], Canada [153], and the international Global Longitudinal Study of Osteoporosis in Women (GLOW) [154] have all reported significant reductions in health-related quality of life among individuals who have suffered fragility fractures at all skeletal sites. Accordingly, a robust clinical case exists for primary prevention of all major osteoporosis fractures, defined as hip, clinical vertebral, wrist or proximal humerus fractures.

To close this gap, pragmatic approaches to case-finding individuals at high risk of suffering these fractures as their first fracture should be adopted, these include:

- Gap 2: Osteoporosis induced by medicines: systematic case finding of individuals at high fracture risk in this group
- Gap 3: Diseases associated with osteoporosis: systematic case finding of individuals at high fracture risk in this group
- Absolute fracture risk calculation: systematic application of tools such as FRAX® to risk stratify the older population

This is supported by most clinical guidelines which cover both secondary and primary fracture prevention

### Closing Gap 5: Adherence to Therapy

Similar to other chronic, asymptomatic diseases, adherence to osteoporosis therapies is poor. The reasons for suboptimal adherence are multiple but include fear of possible side effects, dosing requirements, and an unwillingness to take a medication for a “silent” disease. Two measures of adherence to treatment are commonly used in studies:

- Persistence: Defined as either the time to treatment discontinuation or as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g., 30, 60 or 90 days).
- Compliance: Defined as the ability of a patient to adhere to the dosing, timing, and conditions described by the prescriber or in accordance with the medicine's patient information leaflet. One measure of compliance is the medication possession ratio (MPR). MPR is usually defined as the number of days of medication available to the patient, divided by the number of days of observation.

In routine clinical practice, both persistence and compliance with osteoporosis treatment are sub-optimal, a phenomenon previously reported

for other classes of widely used medicines including antihypertensives [155] and statins [156]. Approximately half of patients initiated on osteoporosis treatment do not follow their prescribed treatment regimen and/or discontinue treatment within a year [157]. This is particularly notable on account of the flexibility of dosing options of widely available osteoporosis treatments, which can be taken as daily, weekly, or monthly tablets, or as daily, quarterly, six-monthly, or annual injections. Intravenous or sub-cutaneous routes of administration provide a means to ensure 100% adherence with treatment, as long as a robust system is in place to administer the initial injection and reliably arrange follow-up injections at appropriate intervals. It has been estimated that improved adherence in the United States would reduce fracture rates by 25%, equating to approximately 300,000 fewer fractures per year and generate savings of US\$3 billion [158].

In a trial to close the gap, in 2013, the Medication Adherence and Persistence Special Interest Group of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) undertook a systematic literature review of interventions to improve osteoporosis medication adherence [159]. Interventions identified which may improve adherence were:

- Simplification of dosing regimens
- Electronic prescriptions
- Patients' decision aids
- Patient education

Patients were most persistent with medications which had the least frequent dosing regimens [160–162]. The use of electronic prescriptions in combination with verbal counselling was associated with a 2.6-fold improvement in short-term compliance compared to verbal counselling alone [163]. A study from the United States evaluated the use of a patient decision aid in combination with usual primary care practice compared to usual primary care practice alone [164]. While adherence at 6 months was similar for both groups, the proportion with more than 80% adherence was significantly higher with the decision

aid. With regard to the impact of patient education, it should be noted that the largest and least biased studies reviewed showed only marginal improvement in adherence [165–168].

The impact of FLS on adherence has been evaluated in several studies [169–173]. Among patients managed by an FLS after fracture, between 74% and 88% remained on treatment at 12 months, and between 64% and 75% at 24 months. These data reinforce the notion that a ‘teachable moment’ exists after individuals have suffered a fragility fracture which can be capitalized upon by an FLS to improve adherence to treatment.

### **Closing Gap 6: Public Awareness of Osteoporosis and Fracture Risk**

Over the past 2 decades, a number of studies have been undertaken to characterise the awareness of osteoporosis and fracture risk among older people. In 2008, investigators from a non-profit Health Maintenance Organization (HMO) in the Northwest United States sought to evaluate key stakeholder perspectives on osteoporosis care after a fracture [174]. These stakeholders included fracture patients, quality and other healthcare managers, primary care physicians, and orthopaedic clinicians as well as staff. Both patients and primary care physicians commented that confusion of osteoporosis with osteoarthritis was common. Furthermore, this confusion led to the perception that osteoporosis is a benign consequence of ageing.

In 2010, Canadian investigators evaluated osteoporosis knowledge among older fracture patients who were treated by orthopaedic surgeons at two major teaching hospitals in Ontario [175]. Fractured patients were asked two questions:

1. Do you know what osteoporosis is?
2. If yes, what do you think it is?

The overwhelming majority of respondents (91%, 115/127) said they knew what osteoporosis was. Among these individuals, 75% gave responses that were considered to be correct. Almost 40% of the interview participants completed a ‘Facts on Osteoporosis Quiz’. Notably, less than half (41%) of those who took the quiz knew that a person who

had suffered a spine fracture was at increased risk of suffering a fracture in the future as compared to a fracture-free individual.

The international GLOW study compared self-perception of fracture risk with actual risk among more than 60,000 postmenopausal women in 10 countries in Europe, North America, and Australia [176]. Key findings included:

- Among women reporting a diagnosis of osteopenia or osteoporosis, only 25% and 43%, respectively, thought their risk was increased.
- Among women whose actual risk was increased based on the presence of any one of seven fracture risk factors, the proportion who recognized their increased risk ranged from 19% for smokers to 39% for current users of glucocorticoid medication.
- Only 33% of those with at least 2 risk factors perceived themselves as being at higher risk.

To close the gap, efforts to improve awareness need to provide clear, evidence-based messages.

Disease awareness campaigns (DACs) such as 2Million2Many from the NBHA in the United States provided an innovative example of implementing this approach [177]. The key messages for 2Million2Many are very simple and compelling:

- Every year, there are two million bone breaks that are no accident (in the USA).
- They are the signs of osteoporosis in people as young as 50.
- But only 2 out of 10 get a simple follow-up assessment.
- Together we can break osteoporosis before it breaks us. But we must speak up. Remember: Break a bone, request a test.

The main target of the disease awareness campaigns is to drive awareness throughout the population of the world that fracture begets fracture. If all individuals aged 50 years or over know that suffering a first fragility fracture significantly increases their risk of suffering second and subsequent fractures, up to one half of all people who will suffer hip fractures in the future could be aware of that risk, and be proactive in taking steps to lower it.

## **Closing Gap 7: Public Awareness of Benefits Versus Risks of Osteoporosis Treatment**

Numerous RCTs and Cochrane Collaboration systematic reviews have demonstrated the efficacy and safety of treatments for osteoporosis. However, in the last decade use of these treatments among individuals at high risk of fracture has been significantly impacted by reports relating to rare side effects, including osteonecrosis of the jaw (ONJ), atrial fibrillation (AF), and atypical femur fracture (AFF).

Earlier studies documented that the risk-benefit calculation for the treatment of osteoporosis among individuals who are at high risk of suffering fragility fractures, including life-changing and life-threatening hip fractures, significantly favours treatment [80, 178, 179]. Patients at risk of osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years [180].

To close the gap, public awareness of osteoporosis must be increased dramatically throughout the world. Effective disease awareness campaigns are needed to ensure that when an older person sustains a fragility fracture, their first thought – and that of their family and friends – is: ‘Did that bone break because of osteoporosis?’ Health professionals and their organisations, national patient societies, health system leaders, and regulatory agencies must work together to craft clear, balanced communications concerning the benefits and risks of treatments. In concordance, both clinicians and patients need to be able to objectively discuss and evaluate the risk-benefit calculation for the patient’s individual circumstances when making collaborative treatment decisions. Having ready access to absolute fracture risk calculation tools such as FRAX® can make such discussions far more tailored – and meaningful – to individual patients. It requires all those involved in the care of osteoporosis patients to ensure clear, balanced communication of these issues – to – individual patients and more widely when opportunities arise.

## **Closing the Gap 8: Access and Reimbursement for Osteoporosis Assessment and Treatment**

During the last decade, IOF has undertaken a series of regional audits throughout the world [181–186]. These audits have evaluated epidemiology, costs, and the burden of osteoporosis in the regions, and have included an overview of access and reimbursement to treatment. Some countries had a very good reimbursement policy for diagnostic tools and therapies, while in other countries there was absolutely no reimbursement available and patients had to pay for all diagnostic tests and treatment.

In the United States reimbursement for treatment varies greatly depending on each patient’s health plan. Health care reform is evolving from fee for service to supporting improved quality, prevention, and care coordination with financial incentives (or penalties) to encourage healthcare professionals and health systems to report on and improve patient outcomes. There are a number of quality measures focused on osteoporosis and post-fracture care but performance around these measures remains low compared to other major chronic diseases. Further, a major drop in reimbursement for DXAs performed in the office setting has led to a drop in the number of providers and more than one million less DXAs performed [93].

## **Closing the Gap 9: Prioritization of Fragility Fracture Prevention in National Policy**

The IOF regional audits provide comprehensive information on the level of priority afforded to fragility fracture prevention by governments throughout the world [181–186].

Osteoporosis guidelines have been endorsed by several governments all over the world; however, there has been quite variation regarding the designation of osteoporosis as a national health priority. The majority of EU states (18/27), as well as most of the developing world, did not recognize osteoporosis or musculoskeletal diseases as a national health priority (NHP).

In the United States, despite a landmark report by the Surgeon General in 2004 and the specific

recommendations from key national and scientific societies intended to prioritize and improve osteoporosis and fracture prevention [187–189], implementation has been poor. Many patients are not given the necessary information about prevention and are not receiving appropriate testing to diagnose osteoporosis or establish osteoporosis risk. Most importantly, a majority of patients who have osteoporosis-related fractures are not being diagnosed with osteoporosis and are not receiving any of the Food and Drug Administration (FDA)–approved, effective therapies.

To close this gap, the provision of robust epidemiological estimates of fracture incidence throughout Asia-Pacific, Central Asia, Latin America, the Middle East, and Africa will be a critical step towards supporting development of fracture prevention policies for these rapidly aging populations.

### **Closing the Gap 10: The Burden of Osteoporosis in the Developing World**

The developing world is set to bear the brunt of the burden of osteoporosis as the world's population rapidly ages during the first half of this century. Accordingly, it is ironic that few data on fracture rates exist in many developing countries. The IOF regional audits provide valuable insights in this regard [181–186].

In Asia, there is an urgent need at the national level to accurately quantify osteoporosis and fracture prevalence in many countries of this region. In eastern Europe and central Asia the lack of solid epidemiological and economic data on the costs and burden of the disease has been linked to the under recognition of osteoporosis status on the side of both the governments and healthcare professionals. Similarly, in Latin America, regional Audit identified a major lack of data on fracture incidence in the region. In the middle east and Africa, The IOF Middle East and Africa Regional Audit identified a major lack of data on fracture incidence in the region in 2011 [186]. Only 6 of the 17 countries in the audit had published hip fracture incidence data. Further,

prevalence rates for vertebral fractures were available for only 3 countries.

To close this gap, all governments need to establish osteoporosis as a national health priority, with commensurate human and financial resources to ensure that best practice is delivered for all.

patients in their jurisdictions. Where the current disease burden is not known, studies to close such evidence gaps must be commissioned forthwith.

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### **Guidelines**

There has been significant development in the guidelines published for the management of osteoporosis. In general, guideline provides recommendations based on current evidence for best practice in the management of osteoporosis and prevention of fractures. It addresses risk factors for fracture, commonly used tools for fracture risk assessment, approaches to targeting therapy, pharmacological, and non-pharmacological treatments to reduce fracture risk in different patient groups, treatment of painful vertebral fractures and systems of care. Sometimes, the assessment and prevention of falls and surgical management of fractures is included.

The most recent guidelines published is the guideline update of the pharmacological management of osteoporosis in postmenopausal women published by the Endocrine Society, USA [190]. The Guideline Update is a document that permits rapid and focused communication to guideline stakeholders in response to new developments that substantially impact the recommendations of an existing clinical practice guideline (e.g., important new drug approval or withdrawal, important new risks or harms). This Guideline Update is published in response to the recent approval of romosozumab by the United States Food and Drug Administration (FDA), the European Medicines Agency, Health Canada, and other agencies; and it represents a formal amendment to the Endocrine Society's recently published clinical practice guideline regarding the pharmacological management of postmenopausal osteoporosis [191].

The guideline for the management of postmenopausal osteoporosis is designed to provide

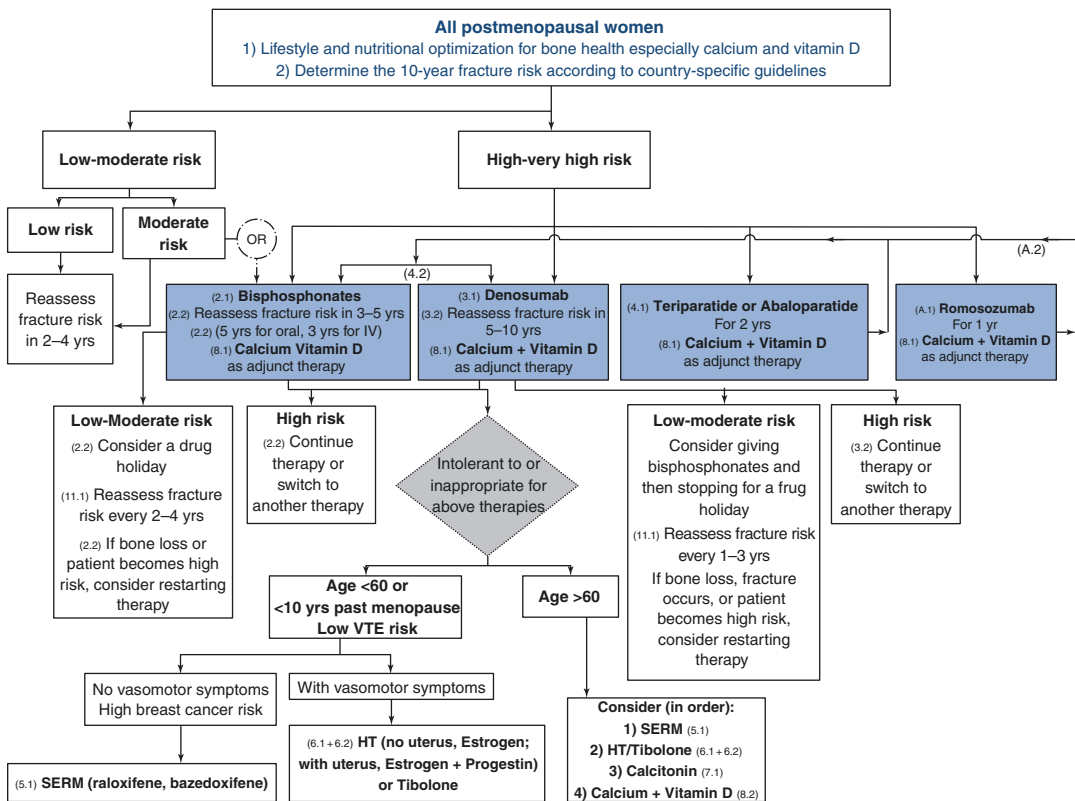


the clinician with an evidence-based approach to the management of this condition. The guidelines (Fig. 21.4) stratify the patients according to their risk of fracture, using that FRAX algorithm, into four risk categories:

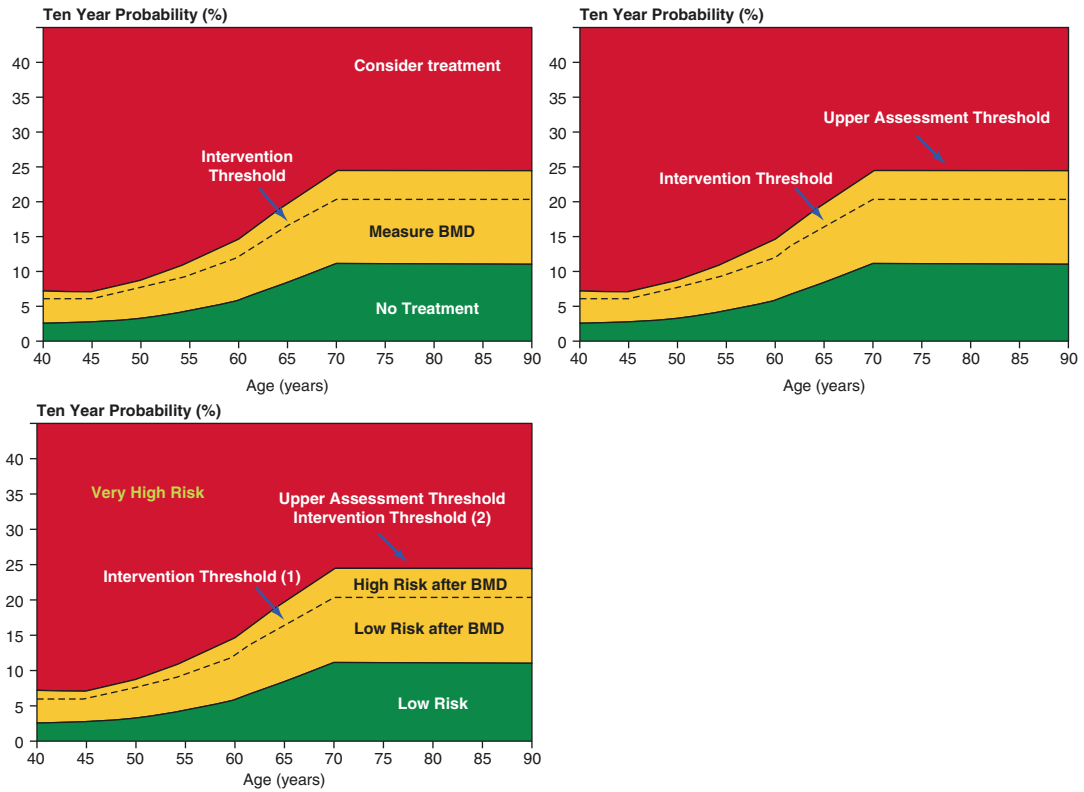
1. *Low risk*: It includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above  $-1.0$ , a 10-year hip fracture risk  $<3\%$ , and 10-year risk of major osteoporotic fractures  $<20\%$ .
2. *Moderate risk*: It includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above  $-2.5$ , and 10-year hip fracture risk  $<3\%$  or risk of major osteoporotic fractures  $<20\%$ .
3. *High risk*: It includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of  $-2.5$  or below, or 10-year hip fracture risk  $\geq 3\%$ , or risk of major osteoporotic fracture risk  $\geq 20\%$ .

4. *Very high risk*: It includes multiple spine fractures and a BMD T-score at the hip or spine of  $-2.5$  or below.

NOGG (UK) provided another approach to stratification of osteoporotic fracture risk combining FRAX risk assessment and BMD measurement (Fig. 21.5). The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two bounds around the intervention threshold where the assessment of BMD will help to determine whether the individual close to the threshold either exceeds that bound or lies below the intervention threshold. These are called assessment threshold for bones. Very high risk is identified as the risk lying above the upper assessment threshold, whereas high risk lies between the intervention threshold and the upper assessment threshold. On the other hand, low risk is reported when the risk lies below the intervention threshold. Figure 21.6 shows a suggested algo-



**Fig. 21.4** Updated algorithm for the management of postmenopausal osteoporosis. (Quoted with permission from the American endocrine society update [190])



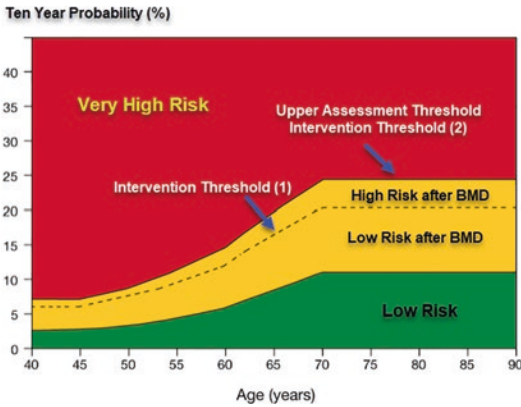
**Fig. 21.5** Infographic outlining of the characterisation of fracture risk by FRAX major osteoporotic fracture probability in postmenopausal women. FRAX probability in the intermediate (orange) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, risk

located in the red zone, above the intervention threshold (2), is identified as “very high risk”, orange zone above the intervention threshold (1) is identified as “high risk,” whereas risk below the intervention threshold (1) or in the green zone is identified as “low risk”

rithm for the management of postmenopausal women adopting the recent recommendations. Recommendation regarding drug holiday and further assessment including repeat FRAX measurement has also been outlined in the guidelines.

In conclusion, this chapter has outlined a step-wise approach to case finding individuals who are at high risk of sustaining fragility fractures. By first closing the secondary fracture prevention care gap, up to half of individuals who would otherwise fracture their hip could be treated to prevent this debilitating and costly injury.

Integration of bone health and falls risk assessments into the management of individuals who take medicines which have adverse effects on bone must become standard practice. Similarly, individuals who are diagnosed with diseases which feature osteoporosis as a common comorbidity need to receive care that will minimise their fracture risk. When the needs of these obviously high-risk groups have been addressed, we must turn our attention to the development of cost-effective strategies to prevent the first major osteoporotic fracture.



**Fig. 21.6** Case finding and treatment pathways according to the categorisation of fracture risk: updated algorithm for the management of postmenopausal osteoporosis. The determination of fracture risk was carried out based on fracture risk score calculation (e.g., FRAX) and the measurement of lumbar spine and hip BMD. \*Stratification of osteoporotic fracture risk can be based on NOGG (UK) as shown in the figures. The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two intervention thresholds are identified based on FRAX calculation based on BMD assessment. The treatment modality is suggested based on whether the individual either exceeds the intervention threshold or lies below it. Alternatively, using FRAX score alone, the fracture risks can be defined as follows: (1) low risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above  $-1.0$ , a 10-year hip fracture risk  $<3\%$ , and 10-year risk of major osteoporotic fractures  $<20\%$ ; (2) moderate risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above  $-2.5$ , and 10-year hip fracture risk  $<3\%$  or risk of major osteoporotic fractures  $<20\%$ ; (3) high risk includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of  $-2.5$  or below, or 10-year hip fracture risk  $\geq 3\%$ , or risk of major osteoporotic fracture risk  $\geq 20\%$ ; and (4) very high risk includes multiple spine fractures and a BMD T-score at the hip or spine of  $-2.5$  or below [190]. \*\*Continue treatment up to 3 years (IV zoledronate) or 5 years (oral bisphosphonate / denosumab), reassess fracture risk: 1. if low or low-moderate risk, consider drug holiday. Reassess fracture risk every 2–4 years; if bone loss, fracture occurs or patient becomes high risk consider restarting therapy. 2. If high risk, continue therapy after checking for adherence or switch to another therapy. \*\*\*After the completion of the anabolic therapy course, consider giving bisphosphonate, then stopping for a drug holiday. Reassess fracture risk every 1–3 years. If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy

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