



Treatment Considerations for Severe Osteoporosis in Older Adults

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Abstract

Osteoporosis, a chronic metabolic bone disease, increases the predisposition to fragility fractures and is associated with considerable morbidity, high health care cost as well as mortality. An elevation in the rate of incident fragility fractures will be observed proportional with the increase in the number of older people worldwide. Severe osteoporosis is currently defined as having a bone density determined by dual-energy X-ray absorptiometry that is more than 2.5 standard deviations (SD) below the young adult mean with one or more past fractures due to osteoporosis. Nutrition, physical activity and adequate vitamin D are essential for optimal bone strength throughout life. Hormone (oestrogen/sex steroid) status is also a major determinant of bone health. This review explores mechanisms involved in bone homeostasis, followed by the assessment and management of severe osteoporosis, including an overview of several treatment options in older people that range from anti-resorptive to anabolic therapies.

1 Introduction

Populations are ageing. Current estimates place the number of people aged 65 or older at 761 million [1]; this age bracket is the fastest growing worldwide, and for the first time in history, there are more people aged 65+ years than children under 5 years [2]. Life expectancy has increased by over 6 years from 2000 to 2019, to 73.4 years [3], and

Key Points

The number of individuals who have a high risk of fracture is increasing commensurate with an ageing population. However, many people at risk or have sustained an osteoporosis related fracture remain untreated.

A clinical and radiological assessment of primary and secondary fracture risk should form part of a comprehensive geriatric assessment in older people.

Evidence now exists for the anti-fracture effect for a range of anti-osteoporotic agents ranging from anti-resorptive to osteoanabolic therapies that can be considered in older people. Choice of treatment should be based on shared decision making with respect to preference, presence of comorbid diseases, polypharmacy burden, quality of life, social and psychological circumstances. Vitamin D 800–1000 international units and 1200 mg calcium a day are important adjuncts to anti-osteoporotic treatments.

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current population projections estimate that by 2050, people over 65 years will account for 16% of the total population (1.6 billion people), equivalent to one in every six persons [4, 5] whilst the number of people aged over 80 will triple, reaching 426 million. Whilst these milestones are testament to advances in current clinical care, living longer has ramifications on physical and mental health. Especially, the associated morbidity and mortality of non-communicable diseases, such as those affecting the musculoskeletal (MSK) system, is one of the leading contributors to global disease burden [6]. It is estimated that 1.71 billion people live with a MSK disorder [7], and in the UK, MSK conditions currently account for the third-largest area of the National Health Service (NHS) budget, as well as a loss of 30 million working days each year [8, 9]. Not only osteoporosis but also osteoarthritis and sarcopenia constitute the largest portion of MSK disorders.

Osteoporosis, a common metabolic bone disease characterized by low bone mass and disruption of bone micro-architecture, contributes annually to 8.9 million fractures worldwide, leading to reduced physical and psychological health, lower quality of life and shorter life expectancy [10–13]. Osteoporosis is also associated with a high health care cost. For example, in the year 2019, osteoporosis incurred an estimated direct total fracture cost approaching £5 billion in the UK [14]. The prevalence of not only osteopenia and osteoporosis but also sarcopenia, the loss of muscle function and mass, increases with age. In combination with other comorbid conditions and presence of frailty, both older women and men are at increased risk of sustaining fragility fractures, defined as fractures consequent to low energy transfer trauma, such as falling from a standing height or less. In the UK, it is estimated that the lifetime probability of a major osteoporotic fracture is 22% in men and 46% in women. Approximately 549,000 fragility fractures occur each year, equating to over one a minute that are accounted by 105,000 hip fractures, 86,000 vertebral fractures and 358,000 other fractures encompassing fractures of the pelvis, ribs, humerus, forearm, tibia, fibula, clavicle, scapula and sternum.

Hip and vertebral fractures are the most serious of all fragility fractures. Rates of hip fracture increase exponentially from the age of 50 years, with two women for every man affected. Fractures are associated with substantial morbidity, whilst mortality after a hip fracture is greatest in the first 12 months post fracture at a rate approaching 26% and is considerably elevated by the presence of co-morbidity [14, 15]. In the UK, the mean length of stay in hospital following a hip fracture is 20 days, which accounts for half a million bed days each year. Each day, 3600 hospital beds in the UK are occupied by patients who have sustained a hip fracture. Of those independently mobile pre-fracture, around half will require ongoing

assistance with their mobility as well as aspects of activities of daily living.

2 Bone Remodelling

Bone is a multifunctional connective tissue composed of organic and inorganic components including but not limited to collagen, non-collagenous proteins, calcium and phosphorus in the form of hydroxyapatite [16]. There are two main types of bone in the adult skeleton: cortical bone constitutes approximately 80% of the adult bone mass whilst trabecular bone constitutes the remaining 20%. Cortical bone is dense and has a low turnover rate of approximately 3% per year. In contrast, trabecular bone has a turnover rate of approximately 26% per year, has a lower mineral content and is more metabolically active and responsive to hormonal stimuli [17]. Whilst cortical bone confers mechanical strength and bone integrity, trabecular bone, found in long bones and vertebrae, undergoes remodelling more than cortical bone, which are the sites most commonly at risk of sustaining fragility fracture [16, 17]. Osteocytes, osteoblasts and osteoclasts are the main cells within bone (Fig. 1). Osteocytes found in the lacunae of the matrix have a mechano-sensory function, and osteoblasts synthesize osteoid whilst osteoclasts enzymatically resorb bone [18]. All three cell types are important for bone growth and remodelling occurring continuously throughout the skeleton in response to mechanical demand, stress or injury that not only shapes skeletal mass, size and shape but also maintains serum calcium and phosphate homeostasis. A remodelling cycle on the bone surface occurs through five sequential stages: activation, resorption, reversal, formation and termination and involves coordinated actions of osteoclasts with osteoblasts [19].

Systemic regulators of bone remodelling, such as the sex steroids, act in concert with local regulators such as cytokines and growth factors including but not limited to sirtuins, protein kinases such as mechanistic target of rapamycin (mTOR), Forkhead proteins, M-CSF, wnt and the RANK/RANKL/OPG system to maintain bone homeostasis. Oestrogen has a significant role in preventing bone resorption by inhibiting osteoclasts [20, 21]. Sclerostin, a key glycoprotein secreted by osteocytes is a potent inhibitor of osteoblastogenesis and bone formation [22, 23]. In midlife/post menopause and later in men, this homeostatic balance between formation and resorption is disrupted. Alterations in cellular activity, i.e. increased osteoclastic activity, will lead to increased bone resorption and decreased bone formation, resulting in a net loss of bone. Bone volume and mass decline in older individuals and in all ethnicities. An imbalance in remodelling within the microenvironment in older people is also driven by mesenchymal stem cell (MSC) senescence and a shift in differentiation to favour

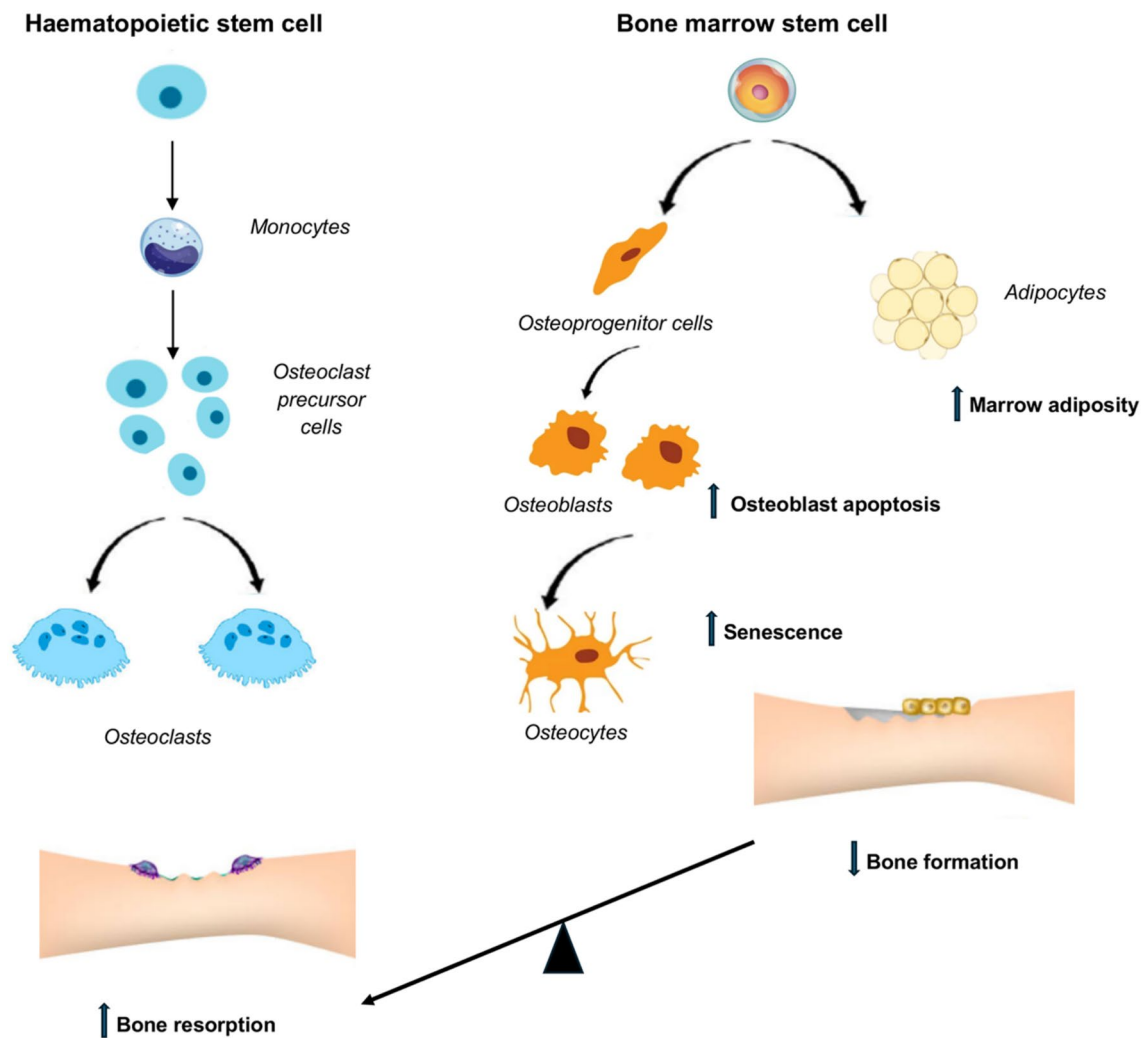


Fig. 1 Resorption dominates over formation, driven in part by increased osteoblastic apoptosis, osteocyte senescence and an increased predilection for bone marrow stem cells to differentiate into adipocytes in older people. Osteoclasts originate from haematopoietic stem cells and degrade bone via secretion of acids and proteolytic enzymes that dissolve collagen and matrix proteins during bone resorption. Osteoblasts arise from committed mesenchymal precursor

cells. Osteoblasts produce extracellular proteins, alkaline phosphatase and collagen—collectively known as the bone matrix, which at first is unmineralized osteoid that subsequently accumulates calcium phosphate in the form of hydroxyapatite. A subpopulation of mature osteoblasts further differentiate into osteocytes within the mineralized bone.

adipogenesis within the bone marrow at the expense of osteoblast generation (Fig. 1) [24]. Consequently, not only trabecular but also cortical thinning, as well as increased cortical porosity, contributes to lower bone quality and strength, and unless this imbalance is disrupted by intervention(s), higher fracture risk at all sites in older people of both sexes will be observed.

3 Osteoporosis in Context of the Lifecourse

When considering the lifecourse, the concept of peak bone mass, defined as the maximum amount of skeletal tissue an individual will have in their life at the termination of skeletal maturation, is thought to be attained between 25 and 30 years of age, and males attain higher bone mineral density (BMD), compared with females [25]. ‘Bone health’ in older age is, therefore, a function of the ‘peak’ attained in early life and the extrinsic and intrinsic changes operating through middle years into old age. Conditions which hinder an individual’s ability to maximize peak adult bone mass, such as undernutrition, inter-current illness and socioeconomic

deprivation, and also low levels of physical activity could, therefore, increase the probability of developing osteoporosis in later in life. Similarly, in later life, lifestyle factors such as steroid use, malabsorption syndromes (e.g. coeliac disease), anorexia, malnutrition, smoking, excess alcohol intake and physical inactivity, as well as other intrinsic and extrinsic risk factors, all contribute exponentially to the increase fracture risk in older people, more so in those with lower peak bone mass [26].

Bone mass decreases at a rate of 0.5% a year after peak levels are attained. Women have an increased risk of primary osteoporosis as they reach a lower peak bone mineral density compared with men, but this risk is further increased by the post-menopausal decline in oestrogen. Bone loss in women is most evident in the trabecular vertebral bodies as they are more metabolically active and are sensitive to oestrogen. Thus, women aged 50 years or over have a four-fold higher rate of osteoporosis and two-fold higher rate of osteopenia than men [11]. However, it is noteworthy that approximately 20% of men who have osteoporosis also live with lower sex steroid levels highlighting requirements for detailed serum investigations as part of a holistic assessment [26]. The general observation of morbidity from osteoporosis and associated fractures in women probably reflects their longer life expectancies.

4 Osteoporosis: Diagnosis and Management

4.1 Diagnosis

Osteoporosis is most often underdiagnosed and undertreated as it progresses without symptoms unless the patient presents with a fragility fracture usually at an older age or a routine clinical assessment concludes information on bone health is needed. Dual-energy X-ray absorptiometry (DXA) to determine bone densitometry is the gold standard method for diagnosing osteopenia and osteoporosis. DXA also provides the opportunity for vertebral fracture assessment (VFA). VFA in conjunction with plain radiography has been recommended by the International Osteoporosis Foundation (IOF) and adopted UK National Osteoporosis Guidelines Group (UK NOGG) as well as the Royal Osteoporosis Society (ROS) to be used in high-risk individuals to detect moderate or severe vertebral fractures and identify those who are at risk of further fracture in the spine or other skeletal sites. Other risk factors for current and future vertebral fracture include a history of measured height loss, self-reported prior fracture after the age of 50 years, kyphosis and long-term glucocorticoid therapy [27].

The diagnosis of osteoporosis is made using DXA scanning to measure the bone mineral density (BMD) of the proximal femur to obtain a T-score, which represents the

number of standard deviations (SD) a patient's BMD is below the mean reference value of a healthy young female population. A T-score ≤ 2.5 SD below the reference value indicates osteoporosis, and where this is accompanied by one or more fractures, this indicates severe osteoporosis [28]. However, a majority of fractures occur in individuals who have osteopenia, defined by a T-score of between 1.0 and 2.5 SDs below the mean reference value. However, DXA results in older people should be interpreted in context of the presence of degenerative spine disease that can artificially elevate BMD. Conversely, total bone matrix can be markedly lower in osteomalacia [29]. In this condition, there is a defect in mineralization of bone matrix because of vitamin D deficiency, secondary to a variety of causes seen in older people including malnutrition, malabsorption, chronic renal disease and poorer exposure to sunlight, e.g. being housebound.

4.2 Assessment of Risk

Women aged 65 years and above, all men aged between 70 and 75 years and above and younger patients with risk factors should receive a form of osteoporosis risk assessment across health care settings. Age, sex, smoking, alcohol use, previous and family history of a fracture and the use of oral glucocorticoids, history of rheumatoid arthritis and the presence of secondary osteoporosis are data that can be input to calculate the FRAX score. These are relevant risk factors to be considered when assessing an older person's individual fracture risk [29]. This tool estimates the 10-year probability of osteoporotic-related fracture and is externally validated, calibrated and applicable in many countries across the globe (<https://frax.shef.ac.uk/FRAX/>) [30, 31]. The output from FRAX assessment can also be modified by bone mineral density values obtained from DXA at the femoral neck where available. The QFracture and Garvan fracture risk prediction algorithms or calculators are other assessment tools which have shown good predictive value in specific countries/populations but have limited utility in diverse populations [32, 33]. Furthermore, all risk calculators generate a risk score rather than indication for treatment and are not comparable with each other [33]. Knowledge of individual T-scores, other risk factors and ascertainment of patient preferences will inform lifestyle changes and treatment strategies appropriate for the patient through shared decision making (SDM) [34]. This takes into consideration what matters most to the patient, presence of comorbid diseases (e.g. chronic kidney disease (CKD)), consequent polypharmacy burden and their social and psychological circumstances. Patients who have a higher future risk of osteoporotic fracture should be treated according to respective local or national osteoporosis guidelines to reduce their future risk.

Given the impact both osteopenia and osteoporosis have on fracture risk, primary prevention through screening and intervention for individuals at high risk could significantly reduce morbidity associated with fragility fractures. The seminal study: screening in the community to reduce fractures in older women (SCOOP) showed that screening with FRAX and pharmacological intervention for postmenopausal women aged 70–85 years at high risk of fracture was associated with a reduction in hip fracture rates. This intervention was also found to be cost-effective compared with the standard care [35].

Older people presenting with a hip fracture are more likely to be osteoporotic, sarcopenic and live with frailty. In these situations, implementing the process of comprehensive geriatric assessment (CGA) by multidisciplinary team, comprising but not limited to orthopaedic surgeons, older people's specialist teams, pharmacy, therapists, nurses, mental health professionals, dietitians, speech and language therapists, is considered best practice [36]. While CGA is the gold standard for patients with hip fracture, input from a multidisciplinary fracture liaison service (FLS) can be beneficial for individuals with other fragility fractures, such as wrist, shoulder or vertebral fractures. FLS are specifically in place to systematically assess, identify and advise on risk factor management to reduce the risk of subsequent, more debilitating fractures [37]. General principles employed by the FLS include preserving bone mineral density through recommending pharmacological and non-pharmacological interventions, such as improving muscle strength and balance, managing falls and other risk factors. Global initiatives such as the International Osteoporosis Foundation's Capture the Fracture initiative (capturethefracture.org) support the expansion of FLS widely within the hospital setting.

Another important concept is the 'imminent fracture risk,' which highlights individuals at high risk of fracture within 12–24 months after a sentinel fracture. For example, in a study of 377, 561 older women ≥ 65 years who had sustained a vertebral and non-vertebral fracture, the cumulative risk of subsequent hip and other fractures at 2 and 5 years was 18% and 31%, respectively [38]. Imminent risk of fracture in older people is elevated by recent prior fracture, fracture site, biological sex, age, osteoporosis and comorbidities such as cognitive dysfunction, polypharmacy, reduced physical activity, poorer general health and falls [39]. This concept emphasizes the importance of early identification, assessment and treatment of those at high risk to reduce future morbidity and mortality from fracture [40, 41].

Several illnesses as well as drug treatments associated with osteoporosis (secondary causes of osteoporosis) are listed in Table 1 and serve as a reminder to clinicians to address these risk factors when conducting their comprehensive geriatric assessment, medicines rationalization or therapeutic deprescribing with the ultimate aim of halting

the progression towards the severe category of osteoporosis [42–50].

4.3 Non-pharmacological Options Supporting the Treatment of Severe Osteoporosis

Physical inactivity in older age translates to decreased mechanical loading on bone that reduces the stimulus on osteoblasts resulting in reduced OPG secretion and increased expression and secretion of RANKL, as well as the pro-inflammatory interleukins IL-1, IL-6 and TNF- α . The combined effect of this imbalance is increased osteoclast differentiation, formation and activity with ensuing bone resorption [26] and low bone mass. Conversely, physical activity stimulates bone growth and preserves bone mass. Physical activity and exercise to correct biomechanical imbalance in the abdominal trunk as well as to strengthen hip flexion and knee flexion is recommended to reduce the risk of falls and for the prevention of osteoporosis. In addition to preserving skeletal muscle, resistance exercise has been shown to increase bone strength through repeated mechanical loading, thereby improving bone mineral density [51]. In support of this notion, a systematic review of 59 studies (20 randomized controlled trials (RCTs)) composed of 1560 participants pertaining to the effect of physical activity on the prevention of osteoporosis in individuals ≥ 65 years concluded that physical activity is very likely to

Table 1 Secondary causes of osteoporosis relevant for older people

Endocrine	Gastrointestinal disorders
Hypogonadism	Malabsorption
	Inflammatory bowel disease
Oestrogen deficiency	Chronic liver disease
Cushing's disease	Eating disorders
Hyperparathyroidism	
Vitamin D deficiency	Others
Growth hormone deficiency	Rheumatoid arthritis
Diabetes	Ankylosing spondylitis
	Multiple sclerosis
Haematological disorders	Sarcopenia
Multiple myeloma	Drug/toxin related
Chronic haemolytic anaemia	Alcohol
	Anti-epileptic drugs
Connective tissue disorders	Androgen deprivation therapies
Ehlers–Danlos syndrome	Glucocorticoids
Marfan's syndrome	Heparin
	Proton pump inhibitors
	Selective serotonin reuptake inhibitors (SSRI)
	Tobacco smoking
	Thyroxine

be beneficial, where increases in BMD were reported more at the lumbar spine over the femoral neck. Furthermore, increases in BMD were more pronounced when multiple as well as resistance exercise regimes were employed [52]. In another systematic review of 43 randomized controlled trials, the most effective type of exercise for increasing femoral neck bone mineral density was high force exercise, such as progressive resistance strength training of the lower limbs [53]. The effect of exercise training on increased BMD at the femoral neck, lumbar spine and trochanter in older postmenopausal women between 60 and 82 years was seen in a further systematic review and meta-analysis of 53 RCTs comprising 2896 participants [54].

Exercise programmes should be personalized to the patient to ensure that they are safe, sustainable and reproducible, e.g. avoidance of sudden rotational movements or severe flexion of the spine to reduce the risk of vertebral compression. Holistic reviews focusing on addressing footwear, home environment and polypharmacy with particular attention to medications with a high anti-cholinergic burden and deprescribing are also key components of assessment of an older person at risk of fracture [55–57]. Furthermore, smoking cessation, avoiding excess alcohol and optimizing nutrition are modifiable factors contributing to the management of osteoporosis.

4.4 Treatments Used to Manage Severe Osteoporosis

4.4.1 Calcium and Vitamin D

Dietary or supplemental calcium is essential for bone mineralization. Bone also acts as a calcium reservoir, restoring physiological levels when serum calcium is low through the action of parathyroid hormone [58]. For example, when dietary calcium is insufficient to meet calcium demand, i.e. during periods of undernutrition or malabsorption often seen in older people. In addition to ultraviolet B radiation induced synthesis, vitamin D may be obtained from egg yolks, salt-water fish and liver, as well as in supplements purchased in isolation or combined with other vitamins [59–61]. Serum vitamin D (25-OH-D) deficiency (< 25 nmol/L) in older people is common, not only secondary to physiological changes in the ability of the skin to synthesize 25-OH-D but also particularly in those who are malnourished, have chronic kidney disease, are institutionalized or are housebound. Intakes of 1000 mg of calcium in combination with 400 international units (IU) of vitamin D per day are generally recommended [62]. However, recommendations for housebound older people or those living in a nursing home are 800–1000 IU of vitamin D and 1200 mg calcium per day [63] through supplementation either through food

fortification or pharmacologically, restoring serum 25-OH-D levels to at least or above 50 nmol/L [63].

In terms of fracture prevention and effects on skeletal muscle, in a systematic review and meta-analysis of 33 randomized controlled trials (RCTs), comprising 1145 participants, primary use of routine calcium and vitamin D supplements was not associated with lower risk of total, hip, vertebral or non-vertebral fractures in community dwelling older adults [64]. Vitamin D has not been shown to be beneficial in the general population for musculoskeletal health despite basic science studies postulating the physiological effects of vitamin D acting through its receptor on muscle health [63, 65, 66]. In another systematic review and meta-analysis of 81 RCTs comprising 53, 537 participants, vitamin D did not have any effects on fracture prevention or prevent falls [67]. Further systematic reviews and meta-analyses have shown that vitamin D with or without calcium had no effect on muscle strength measures or physical performance, e.g. appendicular lean mass, grip strength or physical performance measures [68, 69]. Calcium intake, although can lead to modest increased in BMD, does not clinically reduce the risk of future fracture [70, 71]. Previous studies of calcium supplementation suggested an increased risk of cardiovascular disease, including myocardial infarction [72]. However, other studies found no association between calcium supplementation and risk of cardiovascular disease [73, 74]. Calcium and vitamin D should be given to older people with insufficiency and who are at risk of or are being treated for osteoporosis, who have sustained a fragility fracture and are prescribed glucocorticoids or other treatments that affect vitamin D metabolism, such as anti-convulsant therapy [75, 76].

4.4.2 Pharmacological Options for the Treatment of Severe Osteoporosis

There are various pharmacological options for the treatment of severe osteoporosis that aim to reduce the risk of primary or secondary fractures depending on assessment of the patient. These include:

- (i) Anti-resorptive therapy—bisphosphonates and denosumab
- (ii) Parathyroid hormone (PTH) analogues
- (iii) Romosozumab

Importantly, strontium ranelate is no longer used worldwide for the treatment of severe osteoporosis given the association with stroke and ischaemic cardiac events.

Anti-resorptive therapy—bisphosphonates (alendronic acid, risedronate sodium and zoledronic acid) Bisphosphonates bind strongly to hydroxyapatite and inhibit osteoclast-mediated bone resorption thereby reducing bone turnover

and increase bone mineral density within 1–2 years of commencement, reaching peak action within 3–4 years [77, 78]. Bisphosphonates have been shown to reduce the risk of hip and non-vertebral fractures, even those living with frailty [79–81]. For example, evidence shows 10 mg of alendronate daily for 10 years increased bone mineral density by 13.7% at the lumbar spine, 10.3% at the trochanter, 5.4% at the femoral neck and 6.7% at the total proximal femur. Observational data suggest a lower mortality risk associated with oral bisphosphonate use in the treatment of osteoporosis after hip fracture [82, 83]. Notably, in the observational study conducted by Sambrook et al. [83] 2005 institutionalized older individuals (mean age 85.7 years) prescribed oral bisphosphates were followed up for 5 years and monitored for incident hip fractures and mortality. Bisphosphonate use was associated with a 27% reduction in death compared with non-users (adjusted hazard ratio 0.73, 95% confidence interval (CI) 0.56–0.94, $P = 0.02$). Similar associations have been observed in several other observational studies. However, caution should be exercised when drawing conclusions on the relationship between bisphosphonate use and mortality due to residual or unmeasured confounding [84].

In a landmark randomized placebo-controlled trial conducted by Lyles et al. [85] involving over thousand patients in each arm, intravenous zoledronic acid (5 mg) was administered up to 90 days after repair of low-trauma hip fractures and repeated yearly for the 1.9-year follow-up. This treatment was associated with a 28% reduction in death from all causes in both men and women ($P = 0.01$). Additionally, zoledronic acid reduced the rate of new clinical fractures compared with placebo (8.6% versus 13.9%), representing a risk reduction of 35%. Furthermore, a lower rate of new clinical vertebral fractures (1.7% versus 3.8%, $P = 0.02$) and rates of new non-vertebral fractures (7.6% versus 10.7%, $P = 0.03$) were observed. Notably, there were no significant reductions in new hip fractures.

Meta-analyses have further explored associations between bisphosphonate use and mortality with varied results. For example, following the observations of Lyles et al., an analysis of eight eligible randomized controlled trials revealed that treatment with bisphosphates amongst other agents including intravenous zoledronic acid and denosumab was associated with a reduced mortality of approximately 11%, justifying the use of anti-osteoporotic agents in older individuals living with frailty and who have a high fracture risk [86]. In another meta-analysis, a non-significant decrease in cardiovascular mortality was observed, while a clinically significant reduced risk of all-cause mortality was found in a diverse patient population, including those with osteoporosis and cancer treated with bisphosphonates (pooled risk ratio (RR) of 48 trials: 0.90, 95% CI 0.84–0.98) [87]. However, a recent metanalysis of 47 placebo-controlled RCTs involving 59,437 participants, which accounted for the use of various

bisphosphonates, geographical region as well as diverse populations, did not demonstrate a reduction in mortality risk [88]. Consequently, the authors recommend continued use of bisphosphonates to reduce fracture risk but that further studies investigating the association between bisphosphonate use and mortality are needed.

There is a paucity of studies examining the anti-fracture efficacy of bisphosphonates in men. One multicentre RCT of zoledronic acid in men aged 50–85 years demonstrated a significant reduction in the rate of vertebral fractures in men with osteoporosis [89]. Given limited evidence from trials, current approaches compare BMD responses as an outcome from treatment with anti-osteoporosis agents in men and women with similar fracture risk. A recent systematic review and meta-analysis of 21 RCTs revealed that bisphosphonates, amongst other anti-osteoporosis agents significantly enhanced BMD at the spine, total hip and femoral neck compared with placebo in men [90]. Therefore, the assessment and management of osteoporosis in men should align with diagnostic and treatment algorithms utilized for women, and this view is supported by a recent consensus guideline from the European Society for Clinical and Economic Osteoporosis, Osteoarthritis, and Musculoskeletal Disease (ESCEO) [91].

Alendronate 10 mg once daily or 70 mg once weekly or risedronate sodium 5 mg once daily or 35 mg once weekly is recommended for postmenopausal women and men over 50 years of age, who have confirmed osteoporosis on DXA. Reevaluation of BMD is usually recommended between 3 and 5 years. Thereafter, treatment is continued for up to 10 years if the patient continues to be at risk of fracture or has commenced on corticosteroid therapy. On review, if the T-score is > -2.5 , a drug holiday ranging 1–2 years may be recommended pending further evaluation of BMD and fracture risk [92]. However, discontinuation of bisphosphonates in women at this time may be associated with up to 40% higher risk of new clinical fractures compared with those who continue bisphosphonates, and alternatives should be considered as part of risk factor assessment and shared decision making [93].

Adverse effects of oral bisphosphonates include gastrointestinal symptoms, bone/joint pain, oesophageal ulceration and, rarely, osteonecrosis of the jaw (ONJ). The risk factors for ONJ include concurrent duration and treatment for cancer, smoking and poor dental hygiene. In the absence of cancer, i.e. for the treatment of osteoporosis, the risk of ONJ is minimal, estimated at around 1 in 100,000. Risk factors include chronic ear infections, recent ear operation or suspected cholesteatoma [94]. Atypical femoral fractures (AFF)—atraumatic transverse fractures of the lateral subtrochanteric femur requiring surgical fixation—can occur after prolonged use of bisphosphonate with a rate approaching 1.74 fractures per 10,000 person years for women over

50 years [95]. In a North American study, the risk of AFF increased with longer duration of bisphosphonate use. Hazard ratio compared with less than 3-month use increased from 8.86 (95% CI 2.79–28.20) for 3–5-year use to 43.50 (95% CI 13.70–138.15) when bisphosphonates were used for 8 years or more. Discontinuation of bisphosphonates in this study was associated with a rapid decrease in AFF rate [96]. Similar findings were also observed in a study conducted in Denmark where prolonged use of bisphosphonates was associated with a seven-fold increase in AFF in adults $\geq$ 50 years [97]. Importantly, in this study oral glucocorticoid use and proton pump inhibitor use were independently associated with increased AFF risk—drugs that are commonly used by older people. Oral bisphosphonates should be taken on an empty stomach, in an upright position, with a glass of water [98]. Adherence to bisphosphonates may be challenging in older people because of this complex dosing regime and can be complicated by the presence of polypharmacy, impaired cognition and physical care needs. Furthermore, they should be separated from other medications since they may be mistaken for regular medication and taken concomitantly. In older people with severe gastro-oesophageal reflux, dysphagia or cognitive impairment, alternative preparations, i.e. intravenous (IV) yearly or 18 monthly infusions of zoledronic acid or alternatives to bisphosphonates, may be used [99].

Zoledronic acid is a potent and long-acting bisphosphonate and is licensed for use in the primary or secondary prevention of post-menopausal osteoporosis, not only used in men with osteoporosis but also used in cancer, myeloma and Paget's disease [99]. As an example, intravenous zoledronic acid 5 mg can be used as first line treatment, particularly post-hip fracture repair in hospital. As the rate of incident fracture in the 5-year post-sentinel hip fracture approaches 25% attention to fracture risk reduction is an important priority [38]. In this regard, a single infusion of zoledronic acid was associated with a 23% reduction in fracture by 6 months (hazard ratio 0.77, 95% CI 0.57–1.03, $P = 0.080$) and 25% (hazard ratio 0.75, 95% CI 0.61–0.92, $P = 0.005$) by 12 months [100]. This 20–30-min infusion is an option for older individuals living with advanced frailty or dementia who may be restricted to their own home or have a shortened life expectancy [101, 102]. It is worth noting that intravenous preparations may elicit an acute phase response resulting in fever and myalgia that is short lived and responsive to simple analgesia and dexamethasone [103].

Bisphosphonates are renally excreted and should be avoided in renal impairment. For example, alendronic acid, risedronate sodium and zoledronic acid should be avoided when creatinine clearance is below 30–35 mL/min per 1.73 m^2 . However, it is important to note that eGFR calculations may not be accurate in older people, especially those living

with frailty and sarcopenia. Cockcroft and Gault estimation of GFR is, therefore, necessary to use in these situations.

Denosumab is a humanized monoclonal antibody that blocks RANKL and hence osteoclastic activity within 3 days of administration [77] (Table 2). It is given via a subcutaneous injection (60 mg) on a 6-monthly basis. Even though no dose adjustment is needed in patients with renal impairment, in those with severe renal impairment (creatinine clearance $< 30 \text{ mL/min}$, on dialysis or in individuals with an eGFR 15–29 per min per 1.73 m^2 , the risk of hypocalcaemia is higher, requiring frequent (at least prior to the next dose) monitoring of serum calcium. Thus, supplemental calcium and vitamin D should be taken concurrently. The pivotal Fracture Reduction Evaluation of Denosumab (FREEDOM), multicentre placebo-control trial showed a reduction in fracture incidence of 68% for vertebral fractures, 40% for hip fractures and 20% for non-vertebral fractures, in the first 3 years, in postmenopausal woman taking denosumab [104]. In the 10 year follow-up, a continued lower fracture incidence and an increase in BMD without plateau was observed [105]. Denosumab is often used as an alternative when oral bisphosphonates are not tolerated or are contraindicated or where other social and psychological problems preclude bisphosphonate therapy, e.g. cognitive impairment. Treatment is usually for 5–10 years, after which an assessment of BMD is usually indicated to plan continuation of therapy with another anti-osteoporosis treatment based on specialist recommendation [106]. This is because the anti-resorptive effects of denosumab rapidly diminishes after treatment cessation because of the loss of osteoclast inhibition. [107]. Consequently, fracture risk rapidly returns to pre-treatment levels within 12 months of cessation. Spontaneous rebound vertebral fractures have been documented to occur as early as 7 months after the last dose of denosumab, so 6-monthly patient and physician reminders with clinical and biochemical reviews are of vital importance [108, 109]. This contrasts with bisphosphonates where BMD is maintained for at least 2–5 years after treatment cessation. In FREEDOM, more cases of cellulitis in the denosumab than placebo group were observed, but the overall numbers were extremely small leaving open the question whether the effect was causal or simply a chance finding [110]. Denosumab, similar to bisphosphonates, is also associated with very rare long-term side effects including osteonecrosis of the jaw and atypical femoral shaft fractures.

When initiating denosumab or other anti-resorptive therapy, it is important to ensure that patients have any necessary dental checks or tooth extractions performed, have normal serum calcium levels and are replete in serum 25-OH-D at or above 50 nmol/L [31]. This lowers the risk of severe hypocalcaemia during treatment. Multiple loading regimes exist for those who are vitamin D deficient. In clinical practice, a single dose of 100,000 IU of colecalciferol for individuals

Table 2 Main pharmacological interventions for osteoporosis in older adults

Treatment	Indications/advantages	Side effects and contraindications	Guidance	Dosing	Duration of treatment
Calcium and vitamin D	Reduce the risk of hip fracture and of total fracture in those who are deficient Reduces risk of hypocalcaemia during treatment with anti-resorptive agents	Gastrointestinal symptoms and renal stones Contraindicated in pre-existing hypercalcaemia	Housebound older people or those living in a nursing home are advised to take 800–1000 IU of vitamin D and 1200 mg calcium per day	1200 mg of calcium in combination with 800 IU of vitamin D, daily	Lifelong unless contraindicated
Oral Bisphosphonates	Treatment of postmenopausal, male and glucocorticoid induced osteoporosis	Gastrointestinal symptoms Bone/muscle/joint pain Hypocalcaemia Osteonecrosis of the jaw (rare) Atypical femoral fractures Contraindicated in renal impairment creatinine clearance < 35mL/min; conditions impairing gastric emptying (achalasia, oesophageal stricture) and hypocalcaemia	For postmenopausal women and men over 50 years of age, diagnosed with osteoporosis Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L. Tooth extraction if needed, good dental hygiene and well-fitting dentures are recommended	Alendronate 10 mg PO, once daily or 70 mg once weekly Risedronate sodium 5 mg PO, once daily or 35 mg PO, once weekly	5 years followed by fracture risk assessment and history of steroid use that informs continuation for another 5 years or drug holiday of 6 months to 3 years
Intravenous zoledronic acid	Treatment of osteoporosis and steroid induced osteoporosis in men and post-menopausal women Fracture prevention in women with osteopenia of the hip or femoral neck	Gastrointestinal symptoms including oesophagitis Bone/muscle/joint pain Hypocalcaemia Osteonecrosis of the jaw (rare) Atypical femoral fractures Contraindicated in renal impairment creatinine clearance < 35mL/min and hypocalcaemia; caution advised in decompensated heart failure	Give in patients with recent fragility fracture Administer at least 14 days after hip fracture repair Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L	Zoledronic acid 5 mg IV annually or 5 mg every 18 months for fracture prevention in osteopenia	3 years followed by fracture risk assessment that informs continuation for another 5 years or drug holiday
Denosumab	Reduces the risk of vertebral, hip, non-vertebral fractures Increase in BMD without plateau in postmenopausal women, male and glucocorticoid induced osteoporosis and in patients with a risk of fracture	Hypocalcaemia Abdominal discomfort Increased risk of bacterial infections Skin rash Osteonecrosis of the jaw (rare) Atypical femoral fractures	Alongside calcium and vitamin D supplementation Alternative when oral bisphosphonates are not tolerated or are contraindicated Tooth extraction if needed, good dental hygiene and well-fitting dentures are recommended Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L	60 mg SC (6 monthly)	10 year treatment without any drug holidays. Follow treatment with other anti-osteoporosis agents

Table 2 (continued)

Treatment	Indications/advantages	Side effects and contraindications	Guidance	Dosing	Duration of treatment
Teriparatide	Treatment of post-menopausal, male, and glucocorticoid osteoporosis and patients at high fracture risk Recommended for post-menopausal women with severe osteoporosis who have previously experienced a fragility fracture and are at risk of another within 24 months	Nausea Chest pain Pain in limbs Gastrointestinal disorders Headache Dizziness Contraindicated in hyperparathyroidism, Paget's disease, previous bone radiation therapy or malignancies with bony metastases and severe renal impairment	If intolerant or severe side effects occur from first line therapies described Evidence suggests teriparatide use as first line for the treatment of severe osteoporosis in a case-by-case basis Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L	20 mcg SC daily (maximum 24 months)	Up to 2 years, followed by another anti-osteoporotic agent
Abaloparatide	Treatment of post-menopausal osteoporosis and patient with high fracture risk. Lower risks of new vertebral fractures Reduction in risk of non-vertebral, vertebral and clinical fracture	Injection site reactions, dizziness, headache, nasopharyngitis, joint pain, bronchitis and hypertension Contraindicated in patients with open epiphyses, Paget's disease, bone malignancies and severe renal impairment	Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L	80 mcg SC daily for 18 months	Up to 2 years, followed by another anti-osteoporotic agent
Romosozumab	Treatment of post-menopausal osteoporosis and patients with high fracture risk Reduces the risk of vertebral and non-vertebral fractures	Cardiovascular and cerebrovascular events seen in pivotal trials Headache and injection site reactions There is a potential theoretical risk when combined with other drugs that can potentiate hypocalcaemia Contraindicated in patients with hypocalcaemia or history of stroke or myocardial infarction in the past year	Ensure patients have normal serum calcium levels have vitamin D level at least or above 50 nmol/L QRISK3 could be calculated when considering treatment	210 mg (2 × 105 mg injections sequentially) SC into the abdomen, thigh or upper arm monthly for 12 months	12 months, followed by sequential treatment with another anti-resorptive agent

BMD bone mineral density, IU international units, mg milligrams, mcg micrograms, DXA dual-energy X-ray absorptiometry, PO per oral, IV intravenous, SC subcutaneous

who have sustained a fragility fracture, e.g. of the hip, appears to be well tolerated. This should be then followed with a combination supplementation with calcium and vitamin D (800–1000 IU of vitamin D and 1200 mg calcium).

Alternative loading regimens include 20,000 IU three times a week for a total of 6–7 weeks, followed by 800–1000 IU/day to maintain a serum vitamin D level at or above 50 nmol/L [111]. Vitamin D in excess is associated with hypercalcemia, hypercalciuria and mineral deposits in soft tissues. Importantly, analyses of supplementation studies of vitamin D and calcium by Dawson–Hughes shows a non-linear, U-shaped association between 25-OH-D levels, falls and fracture. The association with increased morbidity appears to occur at higher serum values approaching 100–150 nmol/L, suggesting caution must be exercised when ongoing intermittent high bolus doses of vitamin D are prescribed for an older person. Global data are needed on these associations to inform more precise estimates, but the notion that higher levels of serum 25-OH-D contributes to increased falls and fracture rates is a relevant and important consideration during clinical assessment, treatment and follow-up [63]. The postulated mechanism for increased musculoskeletal morbidity from high bolus doses involves down regulation of 1- α -hydroxylase activity leading to reductions in 1,25 dihydroxy-vitamin D activity, decreased calcium absorption, increased bone turnover and bone loss [76, 112].

Parathyroid hormone analogues (teriparatide and abaloparatide) Teriparatide, a synthetic parathyroid hormone, is anabolic (activates osteoblasts) in bone rather than anti-resorptive and should be administered subcutaneously in the abdomen or thigh at a dose of 20 mcg daily for of 24 months or more in select countries that have approved longer term use. Teriparatide is currently used to treat postmenopausal women with high risk for fracture, men with primary or hypogonadal osteoporosis at high risk of fracture and men and women with glucocorticoid-induced osteoporosis at high risk for fracture [113]. In a seminal randomized placebo-controlled trial with postmenopausal women with at least one prior vertebral fracture, teriparatide was shown to decrease the risk of new vertebral fractures by 65% and non-vertebral fragility fractures by 53%. Furthermore, an increase in BMD was observed at both the lumbar spine (9%) and femoral neck (3%) [114]. It can be used in men and women who are intolerant or who suffer severe side effects from first line therapies described above.

The analyses from the VERtebral fracture treatment comparisons in Osteoporotic women (VERO) trial of the effects of teriparatide and risedronate sodium in postmenopausal women with severe osteoporosis suggest teriparatide can be used first line in those with severe osteoporosis [115, 116]. Teriparatide is contraindicated in patients with metabolic bone diseases such as Paget's disease, skeletal metastases, previous bone radiation therapy and severe renal

impairment. BMD gains are noticeable after 3 months of commencement and last 1–2 years after cessation of teriparatide where a switch to another agent becomes necessary. Side effects may include skin reactions, nausea, arthralgia, headache, dizziness and gastrointestinal symptoms.

Abaloparatide is an analogue of parathyroid hormone-related peptide, is dosed at 80 mcg once daily for a maximum duration of 18 months and is given subcutaneously. It is associated with lower risks of new vertebral fractures when compared with both placebo. Additionally, a lower risk of non-vertebral fractures in comparison with placebo and a significant increase in BMD amongst 2463 post-menopausal women aged 49–86 years in the ACTIVE study was observed. Furthermore, analysis of data from the ACTIVE trial suggested a lower number needed to treat to prevent one vertebral or non-vertebral, clinical or major osteoporotic fracture for abaloparatide compared with teriparatide, suggesting better efficacy compared with teriparatide [117, 118]. The ACTIVEExtend study, where alendronic acid was administered for 24 months after the initial 18 months of abaloparatide, found that this treatment sequence increased BMD as well as reduced the risk of vertebral, non-vertebral, clinical and major osteoporotic fractures in the participants [119]. Finally, a randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of abaloparatide in men and showed significant increases in BMD at the lumbar spine, total hip and femoral neck compared with placebo. Adverse effects may include injection site reactions, dizziness, nasopharyngitis, joint pain and headache [120] (Table 2).

Romosozumab Romosozumab is a monoclonal anti-sclerostin antibody that has both anabolic and anti-resorptive effects that is cleared by hepatic proteolysis and not by the kidneys [77]. Administration is via two 105 mg subcutaneous injections into the abdomen or thigh, totalling a monthly dose of 210 mg for a maximum of 12 months. Significant gains in BMD are typically observed within 6 months of starting treatment and can be maintained post treatment cessation by an anti-resorptive agent. It is generally well tolerated, with 4–5% of patients experiencing injection site skin reactions [121]. Other potential reactions include arthralgia, headaches or infections. Supplementation with calcium and vitamin D is recommended, and although romosozumab has a good safety profile in individuals with reduction in renal function, monitoring of serum calcium is recommended in individuals with severe renal impairment [122].

Several clinical trials have evaluated the efficacy of romosozumab. The FRAME study, an international, randomized double-blind, placebo-controlled trial, assessed romosozumab in postmenopausal women aged 55–90 years with osteoporosis. The romosozumab group had a 75% lower risk of new vertebral fractures at 24 months [123].

The 2018 FRAME extension study further examined the efficacy, safety and fracture risk following 1 year of romosozumab, followed by 2 years of denosumab, and found a lower incidence of fractures in the romosozumab–denosumab group compared with the placebo–denosumab group: new vertebral fractures were 1.0% versus 2.8% ($P < 0.001$), clinical fractures were 4.0% versus 5.5% ($P = 0.004$) and non-vertebral fractures were 3.9% versus 4.9% ($P = 0.039$), respectively [124].

The 2017 ARCH study compared postmenopausal women treated with alendronic acid for 24 months against women who received romosozumab for 12 months followed by alendronic acid for another 12 months. Notably, the romosozumab-to-alendronic acid group demonstrated 48% lower risk of new vertebral fractures ($P < 0.001$) and a 27% lower risk of clinical fractures ($P < 0.001$). The risk of non-vertebral fractures was reduced by 19% ($P = 0.04$), while the risk of hip fracture decreased by 38% ($P = 0.02$) [123, 125].

The STRUCTURE trial in 2017 evaluated the efficacy of romosozumab compared with teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy. After 1 year of treatment, the romosozumab group showed significantly greater increases in areal bone mineral density (BMD) measured by DXA at both the hip and spine. Specifically, the mean percentage change from baseline in total hip areal BMD was 2.6% (95% CI 2.2–3.0) for romosozumab, whereas teriparatide showed a decrease of -0.6% (95% CI -1.0 to -0.2) [126].

The 2018 BRIDGE trial was a smaller randomized placebo-controlled study that found 12 months of romosozumab treatment resulted in significant increases in spine and hip BMD compared with placebo in men with osteoporosis. The mean percentage change from baseline in lumbar spine and total hip BMD was notably higher with romosozumab: 12.1% versus 1.2% for the lumbar spine and 2.5% versus -0.5% for the total hip ($P < 0.001$) [127].

A review of the effectiveness of sequential treatments utilized by FRAME, ARCH and STRUCTURE, by Cosman et al. [128], indicated that initiating treatment with romosozumab for 1 year leads to substantial BMD gains at both the total hip and lumbar spine, suggesting that sequential treatment of romosozumab followed by anti-resorptive agents may be more effective in preventing fractures than the reverse sequence. This ‘anabolic first’ approach could be particularly advantageous for older individuals with severe osteoporosis and is the subject of recent European guidance [129].

There are conflicting findings regarding cardiovascular adverse effects associated with romosozumab. While the FRAME, FRAME extension and STRUCTURE studies found no significant differences in cardiovascular events between the romosozumab and placebo groups, the ARCH

and BRIDGE trials reported an increase in cardiovascular and cerebrovascular events linked to romosozumab use. In the ARCH study, 16 patients (0.8%) in the romosozumab group experienced cardiac ischemic events compared with 6 (0.3%) in the alendronic acid group (odds ratio 2.65, 95% CI 1.03–6.77) and 16 patients (0.8%) in the romosozumab group versus 7 (0.3%) in the alendronic acid group reported cerebrovascular events (odds ratio 2.27, 95% CI 0.93–5.22). The BRIDGE study suggested a numerical imbalance in serious cardiovascular adverse events, with 4.9% of patients in the romosozumab group experiencing such events compared with 2.5% in the placebo group [127, 130]. A potential mechanism for cardiovascular effects was put forward by Zheng et al. [131] postulating that lower sclerostin levels might elevate the risk of hypertension, type 2 diabetes, myocardial infarction and increased coronary artery calcification. However, further research will be necessary to clarify the association between romosozumab and cardiovascular as well as cerebrovascular events [130].

Support for the use of osteoanabolic agents in postmenopausal women was reinforced by a recent network meta-analysis of 69 trials involving over 80,000 patients. The authors concluded that osteoanabolic agents, such as romosozumab and parathyroid hormone receptor antagonists, were more effective than bisphosphonates in preventing clinical and vertebral fractures. Additionally, denosumab treatment was associated with reduced rates of vertebral fractures compared with bisphosphonates [132].

In summary, romosozumab is recommended for postmenopausal women who have sustained a major osteoporotic fracture within the last 24 months but have not experienced a recent stroke or myocardial infarction in the past year. It is suitable for those with a T-score ≤ -3.5 at the hip or spine or a T-score ≤ -2.5 at the hip or spine with either a vertebral fracture, a history of two or more osteoporotic vertebral fractures or high fracture risk indicated by FRAX. From a pragmatic and therapeutic point of view, a QRISK3 calculation to estimate an individual's risk for developing a heart attack or stroke over the next 10 years when considering romosozumab therapy can be conducted to inform clinical decision making [133]. Continuation with either bisphosphonates or denosumab should follow in sequence (Table 2). Further trial data for the efficacy of romosozumab on fracture reduction in men are required.

5 Frailty, Cognitive Impairment, Dementia and Fragility Fracture

Frailty, a syndrome defined as a state of heightened physiological vulnerability to stressors, becomes more prevalent with increasing age and is very often associated with multimorbidity [134]. Physical dysfunction that characterizes

frailty is often seen in parallel with cognitive impairment and or dementia. This cognitive decline is often accompanied by behavioural problems, visual and motor impairments and an increased risk of falls. Moreover, the high prevalence of malnutrition and sarcopenia among patients living with dementia significantly elevates the likelihood of osteoporosis and confers a higher risk for incident and future fractures.

The presence of these conditions presents a unique therapeutic challenge, as this vulnerable group of older people are least likely to receive fracture risk assessments or receive longer-term primary or secondary prevention medications. Several contributing factors contribute to this disparity, including delirium, worsening cognitive decline, institutionalization, poor adherence and competing polypharmacy [135]. Additionally, altered pharmacokinetics due to age and other systemic physiological changes in the body with age increase the risk of adverse drug reactions (ADRs) in this group of patients.

Anti-resorptive and anabolic agents may be prescribed to these patients. Vitamin D and calcium supplementation (800 IU of vitamin D3 and 1200 mg of calcium) has been shown to lower hip and other fracture risk in older female nursing home residents who are deficient [136]. In this regard, CGA can be beneficial for this group of vulnerable patients and can identify achievable goals to improve bone health in the short and medium term, considering the broader medical, social, physical and psychological aspects of their health, including life expectancy [36].

6 Conclusions

The prevalence of osteoporosis rises with age, predisposing to fractures that have significant impact on the lives of older people. Osteoporosis is often underdiagnosed and untreated; therefore, bone and muscle health assessment should be part of a holistic comprehensive geriatric assessment in primary and secondary care. Nutrition, physical activity, exercise, gait and balance interventions benefit both bone and muscle health and can reduce the risk of falls. These interventions should be combined with other lifestyle measures to improve overall bone health. Bone sparing agents are beneficial for fracture risk reduction. But for older people who have a high fracture risk, factors such as frequency, administration route, cost, polypharmacy, ADRs and long-term survival, are key therapeutic considerations. Oral or intravenous bisphosphonates and denosumab have strong evidence for efficacy. Emerging evidence suggests osteoanabolic agents for high fracture risk patients. For those intolerant or unable to use bone sparing agents, vitamin D and calcium can be considered for individuals who are living with frailty, housebound or are in residential care; vitamin D should be offered in

those who are insufficient and if calcium intake is inadequate, and individuals should be encouraged to modify their diet.

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