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OSTEOPOROSIS IN ADULTS: DIAGNOSIS, PREVENTION, AND TREATMENT – A NARRATIVE REVIEW

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ABSTRACT

Objective: To synthesize current evidence on the diagnosis, prevention, pharmacological treatment, and long-term management of osteoporosis in adults.
Methods: PubMed/MEDLINE and reference lists of major guidelines, position statements, systematic reviews, meta-analyses, and pivotal randomized trials were searched, with emphasis on evidence published from 2022 to 2026 and inclusion of older landmark trials when clinically relevant.
Findings: Contemporary assessment integrates dual-energy X-ray absorptiometry (DXA) with fracture history, clinical risk factors, FRAX, vertebral imaging, and evaluation for secondary causes. Prevention combines adequate nutrition, correction of vitamin D deficiency, exercise, fall prevention, smoking cessation, and avoidance of excessive alcohol. Bisphosphonates and denosumab remain major antiresorptive therapies, whereas teriparatide, abaloparatide, and romosozumab are important options for selected patients at very high fracture risk. Treatment sequencing and planned antiresorptive therapy after anabolic treatment or denosumab discontinuation are central to long-term care.
Conclusions: Osteoporosis management should be individualized according to absolute and imminent fracture risk. The principal therapeutic goal is prevention of fragility fractures and preservation of function rather than improvement in BMD alone.

KEYWORDS

Osteoporosis, Bone Mineral Density, Fragility Fractures, Fracture Risk, Osteoporosis Treatment, Osteoporosis Prevention

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Methodology

This narrative review summarizes contemporary evidence on osteoporosis in adults. PubMed/MEDLINE was searched for literature addressing diagnosis, fracture-risk assessment, prevention, pharmacological treatment, monitoring, secondary osteoporosis, and special populations. Reference lists of major clinical guidelines, society position statements, systematic reviews, meta-analyses, and pivotal randomized controlled trials were also reviewed. Priority was given to current clinical guidelines and position statements, systematic reviews and meta-analyses, and pivotal randomized trials. Publications from 2022 to 2026 were emphasized to reflect contemporary clinical practice, while older landmark studies were retained when they established antifracture efficacy or informed long-term treatment and safety considerations. English-language publications relevant to adult osteoporosis were considered, whereas pediatric studies and preclinical evidence were not used to support clinical recommendations. Evidence was synthesized narratively according to the clinical pathway of osteoporosis care, including risk identification, diagnosis, prevention, pharmacological treatment, monitoring, secondary osteoporosis, and future perspectives. Randomized controlled trials were preferentially cited for treatment efficacy, whereas clinical guidelines and position statements were used primarily for recommendations dependent on clinical context.

1. Introduction

Osteoporosis is a common systemic skeletal disorder characterized by impaired bone strength and increased susceptibility to fragility fractures. Its clinical consequences extend beyond reduced bone mineral density (BMD), as fracture risk is influenced by bone microarchitecture, cortical structure, previous fractures, age, comorbidities, medication exposure, and propensity to fall. Fragility fractures most frequently affect the vertebrae, hip, distal forearm, and proximal humerus and may result in substantial pain, functional impairment, loss of independence, reduced quality of life, and increased mortality, particularly following hip fracture (Morin et al., 2025).

The burden of osteoporosis is expected to increase as populations age. Globally, approximately one in three women and one in five men older than 50 years are estimated to sustain an osteoporotic fracture during

their lifetime (Morin et al., 2025). Osteoporotic fractures therefore represent a major public health problem associated with substantial healthcare utilization and socioeconomic consequences.

The development of osteoporosis is multifactorial. Important risk factors include advanced age, female sex, previous fractures, prior falls, low body weight, parental history of hip fracture, glucocorticoid exposure, smoking, excessive alcohol consumption, reduced physical activity, and chronic diseases associated with impaired skeletal health (Morin et al., 2025; Ebeling et al., 2022).

Although DXA-derived BMD remains central to the diagnosis of osteoporosis, BMD alone does not capture the entirety of skeletal fragility. Fragility fractures may occur in individuals whose BMD does not reach the conventional densitometric threshold of osteoporosis. Contemporary approaches consequently emphasize the integration of BMD with clinical risk factors, previous fractures, vertebral imaging, and validated fracture-risk assessment tools (Khan et al., 2024).

The management of osteoporosis has evolved beyond a uniform BMD-based treatment strategy. Bisphosphonates remain an important first-line option for many patients, while denosumab and osteoanabolic therapies provide additional strategies for selected individuals. Current recommendations increasingly emphasize individualized treatment according to the severity and immediacy of fracture risk. Patients at very high or imminent fracture risk may benefit from treatment strategies designed to achieve rapid fracture-risk reduction rather than automatically beginning with a conventional antiresorptive agent (Cosman et al., 2024).

Despite the availability of effective diagnostic and therapeutic interventions, osteoporosis remains substantially underdiagnosed and undertreated. The gap between evidence-based recommendations and clinical practice is particularly important after fragility fractures, when the risk of subsequent fractures is increased. Systematic approaches to fracture identification, risk assessment, treatment initiation, and long-term follow-up are therefore essential.

The aim of this narrative review is to summarize current evidence regarding the diagnosis, prevention, and treatment of osteoporosis in adults, with particular emphasis on fracture-risk assessment, lifestyle interventions, pharmacological treatment, treatment sequencing, and long-term management.

2. Pathophysiology and Risk Factors

2.1. Bone remodeling and skeletal homeostasis

Bone is a metabolically active tissue that undergoes continuous remodeling throughout adult life. Remodeling involves coordinated cycles of bone resorption and formation and is essential for maintaining skeletal integrity, repairing microscopic damage, and regulating mineral homeostasis. Osteoclasts are responsible for bone resorption, whereas osteoblasts synthesize new bone matrix and contribute to its mineralization. Osteocytes act as important mechanosensory and regulatory cells. With aging and under several pathological conditions, coupling between resorption and formation becomes impaired, leading to a progressive negative bone balance (Morin et al., 2025). Osteoporosis therefore reflects both reduced bone mass and deterioration of bone microarchitecture and material properties.

2.2. RANKL/RANK/OPG signaling

The receptor activator of nuclear factor-κB ligand (RANKL), receptor activator of nuclear factor-κB (RANK), and osteoprotegerin (OPG) pathway is one of the principal mechanisms regulating osteoclast differentiation and activity. RANKL promotes osteoclastogenesis through RANK, whereas OPG acts as a decoy receptor. The clinical importance of this pathway is illustrated by denosumab, which inhibits RANKL.

2.3. Wnt signaling and bone formation

The Wnt/β-catenin pathway is central to osteoblast differentiation and activity. Osteocyte-derived sclerostin inhibits Wnt signaling and suppresses bone formation. Romosozumab targets this pathway by neutralizing sclerostin, thereby increasing bone formation while reducing bone resorption.

2.4. Aging-related skeletal changes

Aging is a major determinant of osteoporosis and fracture risk. Osteoblast function decreases, cortical bone becomes thinner and more porous, and trabecular connectivity deteriorates. Ageing also increases fall risk through muscle weakness, frailty, impaired balance, and comorbidity. Fracture risk therefore reflects both skeletal fragility and falls.

2.5. Estrogen deficiency and postmenopausal osteoporosis

Estrogen deficiency is a major driver of postmenopausal bone loss. The fall in ovarian estrogen increases bone turnover and favors osteoclast activity partly through the RANKL/OPG system. The early postmenopausal period is therefore associated with accelerated bone loss. Estrogen also contributes to skeletal health in men through androgen aromatization and direct estrogen signaling.

2.6. Peak bone mass

Peak bone mass is determined by genetic, hormonal, nutritional, and mechanical factors. Individuals who achieve a relatively low peak bone mass have less skeletal reserve later in life. Osteoporosis prevention should therefore begin before adulthood by supporting adequate nutrition, physical activity, and management of chronic disease.

2.7. Major risk factors

Risk factors include advanced age, previous fragility fracture, parental history of hip fracture, female sex, low body weight, smoking, excessive alcohol consumption, low physical activity, nutritional deficiency, glucocorticoid exposure, and chronic endocrine, gastrointestinal, renal, inflammatory, and hematological disorders.

Table 1. Major risk factors for osteoporosis and fragility fractures

Category	Examples
Non-modifiable	Advanced age; female sex; previous fragility fracture; parental history of hip fracture; genetic predisposition
Hormonal	Menopause; premature ovarian insufficiency; hypogonadism
Anthropometric	Low BMI; low body weight
Lifestyle	Smoking; excessive alcohol; physical inactivity
Nutritional	Low calcium intake; vitamin D deficiency; malnutrition
Medication-related	Glucocorticoids; aromatase inhibitors; androgen-deprivation therapy; selected antiseizure drugs
Disease-related	Hyperparathyroidism; hyperthyroidism; malabsorption; chronic kidney disease; rheumatoid arthritis; hematological disease

3. Diagnosis of Osteoporosis

3.1. Clinical assessment

Assessment should begin with fracture risk rather than BMD alone. History should cover previous fragility fractures, falls, family history, menopausal or gonadal status, glucocorticoids and other drugs, nutrition, physical activity, and comorbidities. Height loss, kyphosis, gait impairment, and muscle weakness may provide additional clues.

3.2. Dual-energy X-ray absorptiometry

DXA remains the principal method for measuring areal BMD. Central measurements are obtained at the lumbar spine and proximal femur. In postmenopausal women and men aged 50 years and older, a T-score of ≤ -2.5 at the lumbar spine, femoral neck, or total hip is consistent with densitometric osteoporosis (Gregson et al., 2025; Shuhart et al., 2024).

3.3. T-score and Z-score

The T-score compares BMD with a healthy young-adult reference population and is used for densitometric classification in postmenopausal women and older men. The Z-score compares BMD with an age- and sex-matched population and is preferred in premenopausal women and men younger than 50 years. A Z-score ≤ -2.0 is described as below the expected range for age.

3.4. Limitations of BMD

BMD does not fully capture bone microarchitecture, cortical porosity, bone material properties, falls, or previous fracture. Many fragility fractures occur in people whose T-score is above −2.5; therefore, BMD should be interpreted in the clinical context (Khan et al., 2024).

3.5. FRAX

FRAX estimates the 10-year probability of major osteoporotic fracture and hip fracture using clinical risk factors with or without femoral neck BMD. FRAX is an assessment tool rather than a diagnostic test, and intervention thresholds differ among healthcare systems (Schini et al., 2024).

3.6. Vertebral fracture assessment

Vertebral fractures may be clinically silent. VFA can identify vertebral deformities with low radiation exposure, while conventional radiography or other imaging may be needed when findings are equivocal. A vertebral fracture is an important marker of skeletal fragility and future fracture risk (Khan et al., 2024).

3.7. Trabecular bone score

TBS provides additional information related to trabecular microarchitecture and may refine fracture-risk assessment in selected patients, but it should not be used as a stand-alone determinant of treatment (Shuhart et al., 2024).

3.8. QCT and opportunistic CT

QCT provides volumetric BMD and can distinguish cortical from trabecular compartments. Opportunistic analysis of routine CT imaging may identify previously unrecognized low bone density, but standardized thresholds and protocols remain limited.

3.9. Laboratory evaluation

Laboratory evaluation may also identify findings that point to alternative diagnoses. Markedly abnormal alkaline phosphatase, unexplained hypercalcemia, renal dysfunction, anemia, or abnormalities in phosphate metabolism may indicate disorders other than uncomplicated postmenopausal osteoporosis. Such findings should be interpreted in relation to the clinical picture and may warrant referral for specialist metabolic bone evaluation.

The intensity of the laboratory work-up should be proportional to the pretest probability of secondary disease. A young patient with a low-trauma fracture and no obvious cause may warrant broader testing than an older patient with typical postmenopausal osteoporosis and no additional clinical clues. This risk-based approach balances the value of finding a treatable secondary disorder against unnecessary testing.

Laboratory testing primarily aims to identify secondary causes and other metabolic bone disorders. A basic work-up may include CBC, calcium, albumin, phosphate, alkaline phosphatase, creatinine/eGFR, liver tests, 25-hydroxyvitamin D, and TSH. Additional testing should be individualized.

3.10. Diagnostic approach

Clinical assessment should also determine whether a previous fracture was caused by low trauma. Fractures of the hip, vertebrae, proximal humerus, and distal forearm are classically associated with skeletal fragility, but the clinical context is more important than an isolated anatomical label. A fracture after a high-energy accident should not automatically be attributed to osteoporosis, whereas a fracture following a fall from standing height can be clinically significant even when the DXA result is not in the osteoporotic range (Khan et al., 2024).

The interpretation of BMD requires attention to the validity of each measured region. Degenerative changes in the lumbar spine, vertebral compression fractures, vascular calcification, and other artifacts can produce an apparently elevated lumbar spine BMD. In such cases, the hip measurement and clinical history may provide a more reliable representation of skeletal status. Longitudinal interpretation is also improved when follow-up is performed on the same instrument and when the least significant change of the facility is taken into account (Shuhart et al., 2024; Gani et al., 2024).

FRAX is particularly useful when treatment decisions are uncertain on the basis of BMD alone. Nevertheless, the standard FRAX model has important limitations. It does not fully characterize the frequency or severity of falls, does not directly account for the recency of fracture, and treats several risk factors as binary

variables despite substantial variation in real-world exposure. Clinical judgment is therefore required when an individual patient appears to be at higher risk than the calculated probability suggests (Schini et al., 2024).

Vertebral fracture assessment deserves special attention because vertebral fractures are frequently asymptomatic. Identification of an occult vertebral fracture can alter both diagnosis and management because it documents skeletal fragility and identifies a patient at increased risk of additional fractures. Existing chest or abdominal imaging may also reveal vertebral fractures incidentally, emphasizing the importance of reviewing previously obtained imaging before ordering new studies (Khan et al., 2024).

Particular attention should be paid to discordance between skeletal sites. Degenerative changes may increase apparent lumbar spine BMD, whereas hip BMD may remain substantially reduced. When measurements are discordant, the clinical history, imaging quality, and validity of individual regions of interest should be reviewed before the treatment decision is made. The same principle applies when previous vertebral fractures or severe osteoarthritis compromise the interpretation of the lumbar spine.

The diagnosis of osteoporosis should therefore be interpreted within the broader clinical framework of fracture prevention. A patient with a very low BMD but few additional risk factors may have a different absolute fracture probability from an older patient with a recent vertebral fracture and only moderately reduced BMD. This is the principal reason why modern guidelines emphasize risk stratification rather than a binary interpretation of the DXA result.

Table 2. Main diagnostic methods in osteoporosis

Method	Main role	Main limitation
Central DXA	BMD measurement and densitometric classification	Does not capture all aspects of bone quality
FRAX	10-year fracture probability	Does not capture every fracture determinant
VFA	Detection of vertebral fractures	Image quality may be limited
TBS	Additional fracture-risk information	Not a stand-alone treatment tool
QCT/opportunistic CT	Volumetric BMD or case finding	Standardization and availability
Laboratory testing	Secondary causes	Not diagnostic for primary osteoporosis

4. Prevention of Osteoporosis and Fragility Fractures

4.1. General principles

Prevention is lifelong and includes optimizing peak bone mass, maintaining skeletal and muscular function, minimizing modifiable risk factors, preventing falls, and identifying high-risk individuals before a major fracture.

4.2. Physical activity and exercise

Weight-bearing activity provides mechanical loading, resistance exercise maintains muscle and may support bone, and balance training reduces fall risk. Exercise interventions have been associated with reduced major osteoporotic fractures, although protocols vary (Hoffmann et al., 2023).

4.3. Calcium

Adequate calcium intake supports bone mineralization and calcium homeostasis. Dietary sources are generally preferred. Supplementation should be individualized and should not replace osteoporosis pharmacotherapy when that is indicated (Rizzoli & Chevalley, 2024).

4.4. Vitamin D

Vitamin D supports calcium absorption, mineralization, and muscle function. Deficiency should be corrected, particularly in high-risk patients, but supplementation alone should not be considered a substitute for antifracture pharmacotherapy.

4.5. Protein and nutrition

Adequate protein supports bone matrix, muscle mass, and physical function. Nutritional assessment is particularly relevant in older, frail, underweight, or malabsorption-associated disease.

4.6. Smoking and alcohol

Smoking and excessive alcohol consumption are modifiable fracture-risk factors and should be addressed as part of comprehensive prevention.

4.7. Fall prevention

Fall prevention should include strength and balance training, gait assessment, medication review, visual assessment, and environmental modifications. Exercise-based interventions reduce fall rates in older adults (Guirguis-Blake et al., 2024).

4.8. Fracture Liaison Services

FLS programs provide coordinated identification, assessment, treatment, and follow-up after fragility fractures. A meta-analysis found lower subsequent-fracture risk with FLS care (Danazumi et al., 2024).

4.9. Prevention across the life course

Prevention should also include avoidance of prolonged immobilization whenever medically possible. Reduced mechanical loading can accelerate bone loss, and hospitalization or chronic illness may simultaneously increase muscle weakness and fall risk. Early mobilization and rehabilitation are therefore relevant components of skeletal care in vulnerable patients.

For individuals with an established indication for pharmacological therapy, lifestyle interventions remain necessary because medication does not prevent every fracture. Regular exercise may improve strength and balance, adequate nutrition supports bone and muscle tissue, and fall-prevention measures address the non-skeletal component of fracture risk. The most effective strategy is therefore multimodal rather than dependent on a single intervention.

Nutritional recommendations should also account for the possibility of inadequate protein and energy intake in older adults. Frailty, sarcopenia, low body weight, and reduced mobility often coexist and may amplify fracture risk. A comprehensive nutritional and functional assessment may therefore be more informative than focusing on a single laboratory concentration.

Table 3. Major components of osteoporosis prevention

Intervention	Main objective
Weight-bearing exercise	Maintain skeletal loading
Resistance training	Maintain muscle and bone strength
Balance training	Reduce fall risk
Adequate calcium	Maintain mineral homeostasis
Vitamin D adequacy	Support calcium metabolism and mineralization
Smoking cessation	Reduce modifiable fracture risk
Avoid excessive alcohol	Reduce skeletal and fall-related risk
Fracture Liaison Service	Prevent subsequent fractures

5. Pharmacological Treatment

5.1. General principles

Treatment should be individualized according to absolute fracture risk, previous fractures, BMD, age, comorbidities, contraindications, expected adherence, and patient preference. Bisphosphonates and denosumab are major antiresorptive options, while teriparatide, abaloparatide, and romosozumab are particularly relevant to selected high- and very-high-risk patients (Qaseem et al., 2025; Cosman et al., 2024).

5.2. Bisphosphonates

Alendronate, risedronate, ibandronate, and zoledronic acid inhibit osteoclast-mediated resorption. In the FIT, alendronate reduced hip fracture risk (RR 0.47), radiographic vertebral fracture risk (RR 0.52), clinical vertebral fracture risk (RR 0.55), and all clinical fractures (RR 0.70) (Black et al., 2000). In HORIZON, annual zoledronic acid reduced morphometric vertebral fractures by 70% and hip fractures by 41% over 3 years (Black et al., 2007).

5.3. Denosumab

Denosumab is a RANKL inhibitor administered every 6 months. In FREEDOM, denosumab significantly reduced vertebral, hip, and nonvertebral fractures (Cummings et al., 2009).

5.4. Denosumab discontinuation

Denosumab should not be stopped without a planned subsequent antiresorptive strategy. Discontinuation is associated with rapid reversal of suppression of bone turnover, loss of BMD, and increased risk of vertebral fractures, including multiple vertebral fractures in susceptible patients (Cummings et al., 2018).

5.5. Raloxifene

Raloxifene reduces vertebral fracture risk but has less robust evidence for nonvertebral and hip fracture reduction. Its principal safety concern is venous thromboembolism (Ettinger et al., 1999).

5.6. Menopausal hormone therapy

MHT prevents postmenopausal bone loss and reduces fracture risk in appropriately selected women. Its use should be individualized according to age, time since menopause, indication, route, duration, and cardiovascular, thromboembolic, and oncological risk (The North American Menopause Society Advisory Panel, 2022).

5.7. Teriparatide

Teriparatide stimulates bone formation when given intermittently. In VERO, new vertebral fractures occurred in 5.4% with teriparatide versus 12.0% with risedronate (RR 0.44), with fewer clinical fractures as well (Kendler et al., 2018).

5.8. Abaloparatide

Abaloparatide is a PTH1-receptor agonist with anabolic activity. In ACTIVE it reduced vertebral and nonvertebral fractures compared with placebo (Miller et al., 2016); subsequent alendronate therapy in ACTIVExtend supported maintenance of skeletal gains with sequential treatment (Bone et al., 2018).

5.9. Romosozumab

Romosozumab inhibits sclerostin and increases bone formation while reducing bone resorption. In FRAME it substantially reduced new vertebral fractures; in ARCH, one year of romosozumab followed by alendronate reduced new vertebral, clinical, nonvertebral, and hip fractures compared with alendronate alone (Cosman et al., 2016; Saag et al., 2017).

5.10. Treatment according to fracture risk

Many patients at high fracture risk can begin with an antiresorptive agent. Selected patients with very high or imminent fracture risk may benefit from an anabolic or dual-action therapy followed by antiresorptive consolidation (Cosman et al., 2024).

5.11. Sequential treatment

Anabolic or dual-action therapy followed by antiresorptive treatment can help maintain skeletal gains. The therapeutic sequence should be considered at the time the initial treatment is selected.

5.12. Safety considerations

Treatment selection should also consider practical factors that affect persistence and safety. Oral bisphosphonates may be less suitable for patients with significant esophageal disease, inability to remain upright after administration, or persistent gastrointestinal intolerance. Intravenous zoledronic acid may be preferable in some patients, although renal function and acute-phase reactions must be considered. Denosumab may simplify administration but requires reliable follow-up because delays in dosing have clinically important consequences.

When selecting an osteoanabolic strategy, the clinician should consider whether rapid improvement in skeletal strength is a priority. Recent or multiple vertebral fractures, a very low BMD, and fractures occurring despite prior treatment may support a higher-intensity approach. The initial choice should nevertheless be

coordinated with the planned subsequent antiresorptive treatment, because discontinuation without consolidation may result in loss of skeletal benefit.

Patient preference should be incorporated into treatment selection. Some patients prioritize oral administration at home, whereas others prefer infrequent injections or infusions. Shared decision-making can improve understanding of expected benefits, potential adverse effects, and the need for long-term follow-up. Treatment choice is therefore the result of both evidence-based risk stratification and individualized clinical judgment.

Oral bisphosphonates require administration on an empty stomach with plain water and a period of remaining upright, which can present practical challenges. Gastrointestinal intolerance may lead to discontinuation, while poor adherence can reduce the real-world benefit of an otherwise effective therapy. Intravenous zoledronic acid avoids gastrointestinal absorption issues but can produce a transient acute-phase reaction, particularly after the first infusion.

Before antiresorptive treatment, clinically important hypocalcemia and severe vitamin D deficiency should be corrected. Renal function is especially relevant to intravenous bisphosphonate treatment. In patients with advanced chronic kidney disease, the diagnosis may overlap with CKD-MBD and the choice of therapy requires more individualized assessment than in uncomplicated postmenopausal osteoporosis.

Medication-related osteonecrosis of the jaw and atypical femoral fractures are rare complications of antiresorptive therapy. Their absolute risk should be discussed in the context of the much greater baseline risk of osteoporotic fractures in appropriately selected patients. Dental health should be optimized and invasive dental procedures should be managed according to clinical need rather than reflexively withholding effective osteoporosis therapy.

Denosumab requires strict attention to the dosing schedule because its antifracture effect is dependent on continued suppression of bone turnover. A missed or delayed dose should prompt active follow-up rather than passive observation. When treatment needs to be stopped, the subsequent antiresorptive regimen should be planned before the final denosumab dose wears off (Cummings et al., 2018).

The evidence for anabolic therapy is strongest in populations with severe osteoporosis or very high fracture risk. Teriparatide and abaloparatide primarily stimulate bone formation, while romosozumab has both anabolic and antiresorptive effects. Their relatively rapid skeletal effects make them attractive when fracture prevention is urgent, but the initial course should be considered part of a longer treatment sequence rather than an isolated intervention.

Cardiovascular risk assessment is particularly important before romosozumab. The ARCH trial reported a numerical imbalance in serious cardiovascular events during the first year, and current treatment pathways generally avoid romosozumab in patients with recent myocardial infarction or stroke. This illustrates the need to evaluate competing clinical risks alongside the anticipated antifracture benefit (Saag et al., 2017).

Renal function is an important determinant of treatment selection. Intravenous bisphosphonates require particular caution in significant renal impairment, whereas denosumab is not renally cleared but may cause clinically important hypocalcemia in patients with advanced chronic kidney disease. In such patients, calcium and vitamin D status and the broader CKD-MBD phenotype should be considered before therapy.

The selection of an antiresorptive agent should consider the fracture sites the clinician is most concerned about preventing. Evidence is particularly robust for hip-fracture reduction with several bisphosphonate regimens and denosumab, whereas some agents have a stronger evidence base for vertebral than for hip or nonvertebral fractures. This distinction is clinically relevant in older adults in whom hip fractures are associated with substantial morbidity, loss of independence, and mortality.

Medication-specific risks include gastrointestinal and renal considerations for bisphosphonates, hypocalcemia and rebound fracture risk with denosumab, hypercalcemia with anabolic agents, and cardiovascular risk considerations with romosozumab.

Table 4. Pharmacological therapies for osteoporosis

Therapy	Mechanism	Key role	Important limitation
Alendronate	Osteoclast inhibition	First-line option for many patients	Oral administration/GI issues
Zoledronic acid	Osteoclast inhibition	Potent IV antiresorptive	Renal considerations; acute-phase reaction
Denosumab	RANKL inhibition	Potent antiresorptive	Planned transition after discontinuation
Raloxifene	SERM	Selected postmenopausal women	VTE risk; mainly vertebral efficacy
MHT	Estrogen replacement	Selected postmenopausal women	Individual systemic risk-benefit
Teriparatide	PTH receptor agonism	Very high fracture risk	Sequential antiresorptive needed
Abaloparatide	PTH1 receptor agonism	Very high fracture risk	Sequential antiresorptive needed
Romosozumab	Sclerostin inhibition	Very high fracture risk	Cardiovascular risk assessment

In clinical practice, the therapeutic decision can be framed around three questions: how high is the patient's fracture risk, how quickly does that risk need to be reduced, and which treatment sequence can maintain benefit over time? This framework helps distinguish patients who are appropriately managed with an antiresorptive-first strategy from those who may benefit from an initial anabolic or dual-action treatment.

6. Monitoring and Long-Term Management

6.1. Monitoring principles

Long-term follow-up should evaluate adherence, adverse effects, new fractures, changes in fracture risk, and BMD when clinically appropriate.

6.2. Follow-up DXA

Repeat DXA should have a clinical purpose and be individualized according to baseline risk, treatment, age, and the probability that the result will alter management (Gani et al., 2024).

6.3. Bone turnover markers

CTX and PINP may provide information about biological response in selected patients, but their variability limits use as stand-alone measures of treatment success.

6.4. Adherence

Poor persistence is common, particularly with oral therapies. Barriers include gastrointestinal effects, complex administration, polypharmacy, and limited symptom burden.

6.5. Bisphosphonate holiday

After several years of bisphosphonate therapy, selected patients whose fracture risk has decreased may be considered for a temporary holiday. FLEX demonstrated that discontinuation after 5 years of alendronate caused some BMD decline but did not increase overall nonvertebral fracture risk; continued treatment benefited some women at higher vertebral-fracture risk (Black et al., 2006).

6.6. Denosumab

A routine drug holiday is not appropriate for denosumab. If treatment is discontinued, an appropriate subsequent antiresorptive strategy should be planned (Cummings et al., 2018).

6.7. Treatment failure

A fracture during treatment does not automatically prove failure. Adherence, administration, secondary causes, calcium/vitamin D status, fall risk, and baseline fracture severity should be reassessed before changing therapy.

6.8. Long-term strategy

Follow-up should also consider whether the patient has achieved the intended therapeutic goal. A stable BMD in a patient who remains free of new fractures may represent an appropriate response to antiresorptive therapy. Conversely, recurrent fractures, especially vertebral fractures, may indicate that a patient remains in a very-high-risk state even if the DXA value has not changed substantially. Treatment decisions should therefore consider the entire clinical trajectory (Cosman et al., 2024).

Bone turnover markers can be useful when a rapid biological response is expected, although they should be measured and interpreted using standardized methods. They can support assessment of adherence or the expected pharmacodynamic effect, but they are not established as stand-alone surrogate endpoints for fracture prevention in routine care.

The possibility of a treatment holiday should be considered only after reassessment of current risk. The presence of a previous hip fracture, multiple vertebral fractures, or persistently very low hip BMD generally argues for continued anti-fracture therapy rather than automatic treatment interruption. Conversely, patients whose risk has become substantially lower after a period of bisphosphonate therapy may be appropriate candidates for a supervised holiday (Adler et al., 2016).

Monitoring should also include confirmation that the treatment plan remains aligned with changes in the patient's health status. A patient may develop a new indication for glucocorticoids, experience recurrent falls, sustain a new vertebral fracture, or develop renal impairment. Each of these events can change the balance between treatment options and may justify modification of the original plan.

Treatment should be continued, modified, sequenced, or temporarily interrupted according to the patient's evolving fracture risk and treatment goals.

Table 5. Principles of long-term management

Clinical situation	General approach
Several years of bisphosphonate therapy	Reassess risk before continuation or holiday
Denosumab discontinuation	Transition to appropriate antiresorptive therapy
Completion of anabolic therapy	Initiate antiresorptive therapy
New fragility fracture	Reassess adherence, secondary causes and treatment intensity
Small DXA change within measurement error	Do not interpret automatically as failure

7. Secondary Osteoporosis and Special Populations

7.1. Secondary osteoporosis

Secondary osteoporosis results from disease, medication, or another identifiable cause. It is especially important in men, younger adults, premenopausal women, severe or atypical disease, and unexpected fractures despite therapy (Ebeling et al., 2022).

7.2. Osteoporosis in men

Men with osteoporosis should be assessed for secondary causes such as hypogonadism, glucocorticoid exposure, alcohol use, renal disease, gastrointestinal disorders, and hematological disease. Bisphosphonates, denosumab, and anabolic therapies are available according to fracture risk (Fuggle et al., 2024).

7.3. Glucocorticoid-induced osteoporosis

Glucocorticoids suppress osteoblast function and may increase early bone resorption, alter calcium metabolism, and increase falls through muscle weakness. The ACR guideline recommends fracture-risk assessment in adults receiving at least 2.5 mg/day prednisone equivalent for more than 3 months (Humphrey et al., 2023).

7.4. Cancer therapy-associated bone loss

Aromatase inhibitors and androgen-deprivation therapy can accelerate bone loss. Risk assessment and bone-protective management should be incorporated into cancer care (Ebeling et al., 2022).

7.5. Chronic kidney disease

CKD-related mineral and bone disorder can coexist with conventional osteoporosis risk. Assessment should integrate kidney function, calcium, phosphate, PTH, alkaline phosphatase, fracture history, and BMD. Treatment requires individualized consideration (Henry et al., 2025; Kidney Disease: Improving Global Outcomes [KDIGO] CKD-MBD Update Work Group, 2017).

7.6. Diabetes mellitus

Type 2 diabetes may be associated with higher BMD despite increased fracture risk, demonstrating the limitations of BMD alone (Brandt et al., 2024).

7.7. Premenopausal women and pregnancy-associated osteoporosis

In younger women, Z-scores are preferred and secondary causes should be sought. Pregnancy- and lactation-associated osteoporosis is rare and requires individualized management because high-quality comparative pharmacological evidence is limited (Hadji et al., 2026).

7.8. Older adults, frailty and sarcopenia

Special populations also illustrate why treatment thresholds cannot always be transferred directly from trial populations to individual patients. In a younger adult, the absolute probability of fracture over the next decade may be lower despite a low BMD, while in a frail older adult a recent fracture may signal a much higher short-term probability of another fracture. Clinical judgment must therefore incorporate both relative skeletal impairment and absolute fracture probability.

In men, cancer therapies, glucocorticoids, hypogonadism, and chronic disease frequently contribute to bone loss. In postmenopausal women, estrogen deficiency is a major driver of bone turnover, but the same patient may also have secondary risk factors such as glucocorticoid exposure or malabsorption. A diagnostic label should therefore describe the clinical syndrome without obscuring its underlying contributors.

In pregnancy- and lactation-associated osteoporosis, treatment decisions may be constrained by pregnancy, breastfeeding, and future reproductive plans. Because evidence is mainly observational, clinicians should individualize the balance between nutritional measures, breastfeeding decisions, pain control, rehabilitation, and pharmacological therapy. The 2026 international position statement highlights the need for coordinated multidisciplinary assessment in these patients (Hadji et al., 2026).

For older adults with multiple comorbidities, treatment decisions should also account for life expectancy, baseline functional status, ability to adhere to therapy, and the practical consequences of a fracture. These considerations do not imply therapeutic nihilism; rather, they support selection of an intervention whose expected benefit is meaningful within the patient's overall goals of care.

Older adults have combined risks from skeletal fragility, falls, frailty, and muscle weakness. Management should therefore integrate pharmacological treatment with resistance exercise, balance training, nutritional optimization, and fall prevention.

8. Emerging Therapies and Future Perspectives

8.1. Evolving treatment paradigm

The field has moved from predominantly antiresorptive therapy toward risk-stratified use of anabolic and dual-action agents and planned sequential treatment (Cosman et al., 2024).

8.2. Sclerostin and Wnt signaling

Romosozumab validates sclerostin inhibition as a clinically effective strategy. Other regulators of Wnt signaling, including DKK1, remain investigational.

8.3. Novel targets

Cathepsin K inhibition and additional Wnt-directed therapies remain areas of research. The discontinuation of odanacatib illustrates the importance of long-term safety beyond BMD improvements.

8.4. Artificial intelligence and opportunistic imaging

AI-assisted detection of vertebral fractures and opportunistic CT-based bone-density assessment may improve case finding, but prospective validation and standardization remain necessary.

8.5. Personalized sequential treatment

Future algorithms may integrate BMD, fracture recency, previous fractures, bone turnover, comorbidities, falls, and previous treatment to individualize therapy sequence.

8.6. Research priorities

Another important area is comparative effectiveness research that evaluates complete treatment sequences rather than individual drugs. Trials of isolated agents answer whether a medication is better than placebo or a comparator during a defined period, but clinical decisions increasingly involve what should happen before and after each treatment phase. Studies that compare anabolic-first and antiresorptive-first strategies over longer periods may therefore provide more clinically useful evidence.

Implementation science is also relevant. Even highly effective medications have limited population-level impact when patients are not identified, treatment is not initiated, or therapy is discontinued prematurely. Future research should consequently assess not only drug efficacy but also pathways that increase diagnosis after fragility fracture, facilitate access to DXA and pharmacotherapy, improve adherence, and ensure appropriate transitions between treatments.

Finally, future osteoporosis research should increasingly include patient-centered outcomes. Prevention of fractures is the principal objective, but preservation of mobility, independence, quality of life, and the ability to remain in the community are highly relevant outcomes for older adults. Economic evaluations should similarly incorporate rehabilitation, long-term care, hospitalization, and productivity losses rather than focusing only on medication costs.

An important future direction is the development of fracture-risk models that better reflect the timing and severity of fractures. A recent vertebral fracture may convey a particularly high short-term risk, and future tools may incorporate fracture recency, multiple fracture locations, and longitudinal changes in BMD rather than relying primarily on static baseline variables.

Another priority is improving the clinical use of existing imaging. Automated vertebral fracture detection on CT, opportunistic bone-density estimation, and integrated electronic health-record algorithms could identify high-risk patients who are currently missed by conventional referral pathways. Implementation will require validated thresholds, attention to false positives and negatives, and demonstration that case finding actually leads to improved clinical outcomes.

Novel pharmacological targets also need to be evaluated beyond their effects on BMD. A therapy that produces a large increase in BMD but an unacceptable cardiovascular or other safety signal cannot be considered clinically successful. Future trials should therefore prioritize fracture endpoints, long-term safety, patient-reported outcomes, and comparative effectiveness.

Major priorities include prediction of imminent fracture risk, safer anabolic therapies, improved adherence, validated technology-assisted diagnosis, and better evidence in secondary osteoporosis and advanced CKD.

9. Discussion

9.1. Principal findings

The evidence supports a shift from a purely BMD-centered model toward integrated fracture-risk assessment. DXA remains essential, but previous fractures, age, comorbidity, medication exposure, bone quality, and falls also influence risk (Khan et al., 2024).

9.2. Treatment gap

Many patients are identified only after fragility fracture and remain without systematic secondary prevention. FLS programs can reduce subsequent fracture risk (Danazumi et al., 2024).

9.3. Pharmacological strategy

Bisphosphonates remain effective and practical for many patients. Denosumab is a potent alternative but requires careful discontinuation planning. Very-high-risk patients may benefit from anabolic-first strategies followed by antiresorptive consolidation.

9.4. Prevention and lifestyle

Lifestyle interventions are foundational but do not replace pharmacological therapy in patients with a clear indication for medication.

9.5. Secondary osteoporosis

Secondary causes should be investigated particularly in younger people, men, severe disease, atypical presentations, and apparent treatment failure (Ebeling et al., 2022).

9.6. Remaining challenges

There is also a need for better evidence in populations that are routinely underrepresented in large randomized trials. This includes younger adults with secondary osteoporosis, men with complex comorbidity, people with advanced CKD, and patients with pregnancy- or lactation-associated osteoporosis. Evidence in these settings is often derived from observational studies, extrapolation from other populations, or expert consensus.

Another unresolved issue is the heterogeneity of fracture-risk thresholds between countries. Tools such as FRAX are calibrated to local epidemiology, while access to DXA, reimbursement policies, and availability of anabolic therapies also vary. As a result, treatment pathways cannot always be transferred unchanged from one healthcare system to another.

Important challenges include underdiagnosis, undertreatment, adherence, inconsistent post-fracture care, incomplete fracture-risk prediction by BMD, and uncertainty regarding optimal long-term sequencing in some populations.

9.7. Limitations of this review

The interpretation of treatment effects should also consider differences between trial populations and routine clinical practice. Many pivotal trials enrolled participants with defined levels of BMD and fracture risk and excluded individuals with substantial comorbidity. External validity may therefore be limited when treatment is applied to frail patients, people with advanced renal disease, or those with multiple interacting secondary causes.

A further limitation is that some recommendations necessarily rely on expert consensus where randomized evidence is limited. This is particularly relevant to treatment sequencing, management of some secondary forms of osteoporosis, and care of pregnancy- and lactation-associated osteoporosis. Accordingly, areas of uncertainty are identified explicitly rather than presented as settled evidence.

Because this is a narrative review, the selected literature emphasizes clinical relevance and influential evidence rather than exhaustive retrieval of every eligible study. This approach is appropriate for a broad overview but means that conclusions should not be interpreted as the result of a formal systematic-review process. The most reliable clinical statements in this article are therefore those supported by contemporary guidelines, position statements, systematic reviews, and pivotal randomized trials.

10. Conclusions

Osteoporosis is a common chronic skeletal disorder in which fracture risk results from the interaction of reduced bone strength and multiple clinical determinants. Although DXA remains fundamental to diagnosis, optimal management requires integration of BMD with previous fractures, clinical risk factors, vertebral imaging when appropriate, and investigation of secondary causes. Prevention should include adequate nutrition, correction of vitamin D deficiency, appropriate calcium intake, regular weight-bearing and resistance exercise, fall prevention, smoking cessation, and avoidance of excessive alcohol consumption. These interventions complement, but do not replace, pharmacological treatment in patients at sufficiently high fracture risk. Bisphosphonates remain an important treatment for many patients, while denosumab, teriparatide, abaloparatide, and romosozumab provide additional options according to individual risk and clinical circumstances. Long-term management requires adherence assessment, appropriate monitoring, individualized decisions regarding treatment duration, and careful planning when therapies are discontinued. Future advances will likely involve improved fracture-risk prediction, more individualized treatment sequences, AI-assisted diagnosis, novel anabolic approaches, and greater integration of bone, muscle, and fall prevention strategies. The ultimate objective of osteoporosis management is not simply to increase BMD, but to prevent fragility fractures, preserve physical function, and reduce fracture-associated morbidity and mortality.

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