WebLog Journal of Gerontology and Geriatrics

Review Article
Published: 14 Feb, 2026

Osteoporosis: Contemporary Understanding, Diagnostic Advances, and Evolving Therapeutic Strategies

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WebLog Open Access Publications
Article ID : wjgg.2026.b1408
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Abstract

Objectives: To synthesise current evidence on the epidemiology, risk factors, diagnostic strategies, and therapeutic approaches in osteoporosis, with emphasis on recent advances in risk stratification, imaging, and pharmacological management such as anabolic therapies, vitamin D analogues such as alfacalcidol, and emerging agents.

Design: Narrative review of contemporary literature, including recent clinical reviews and guidelines.

Data Sources: Peer-reviewed articles and clinical guidelines identified through web search, including BMJ clinical reviews and primary care guidance.

Eligibility Criteria: Articles addressing epidemiology, pathophysiology, diagnosis, fracture risk assessment, and management of osteoporosis.

Results: Osteoporosis is a chronic skeletal disease associated with substantial morbidity, mortality, and economic burden. Hip fractures carry a one-year mortality of approximately 20%. Emerging risk factors include diabetes, sarcopenia, and bariatric surgery. Advances include FRAXplus for refined risk stratification, trabecular bone score, and radiofrequency echographic multi-spectrometry imaging. Management has shifted from BMD-based decisions to fracture-risk–based treatment pathways. Sequential therapy beginning with anabolic agents is increasingly recommended for highest-risk patients. Osteoporosis remains a major global health burden. Advances include improved fracture-risk stratification, novel imaging modalities, and a shift toward risk-based and sequential therapy. Anabolic agents, vitamin D analogues, and emerging biologics have expanded treatment options.

Conclusions: Osteoporosis remains a major public health challenge. Improved risk assessment tools, novel imaging modalities, and evolving pharmacological strategies offer opportunities for more personalised, goal-directed care. A personalised, risk-stratified approach integrating new diagnostics and sequential therapy offers the most effective strategy for reducing fracture burden.

Keywords: Osteoporosis; Fragility Fractures; Vertebral Compression Fractures; Bone Mineral Density (BMD); Trabecular Bone Score (TBS); Radiofrequency Echographic Multi-Spectrometry (REMS); Fracture Risk Assessment; FRAX; Sequential Therapy; Anabolic Therapy; Teriparatide; Abaloparatide; Romosozumab; Antiresorptive Therapy; Bisphosphonates; Denosumab; Vitamin D Analogues; Alfacalcidol; Cholecalciferol; Bone Quality; Imminent Fracture Risk; Sarcopenia; Secondary Osteoporosis; Morbidity and Mortality; Kyphosis; Bone Health in Ageing

Summary Box

What is already known on this topic

- Osteoporosis is defined by low bone mass and microarchitectural deterioration, leading to

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Received Date: *15 Jan 2026*
Accepted Date: *12 Feb 2026*
Published Date: *14 Feb 2026*

Citation:
Zaparackaite I, Singh SJ, Bhattacharya DC, Correia RC, Mehta AR, Midha PK, et al. Osteoporosis: Contemporary Understanding, Diagnostic Advances, and Evolving Therapeutic Strategies. WebLog J Gerontol Geriatr. wjgg.2026.b1408. https://doi.org/10.5281/zenodo.18811618

fragility fractures.

- Hip fractures carry high morbidity and mortality, with a one-year mortality of ~20%.
- Traditional management relied heavily on BMD thresholds.

What this study adds

- Highlights emerging risk factors such as diabetes, sarcopenia, and bariatric surgery.
- Summarises advances in imaging (TBS, REMS) and risk tools (FRAXplus).
- Reviews the shift toward fracture-risk–based treatment and sequential therapy strategies.

Strengths and Limitations of This Review

Strengths

- Integrates recent clinical reviews and guideline-based recommendations.
- Provides a structured, BMJ Open–style synthesis suitable for clinicians and researchers.

Limitations

- Narrative rather than systematic review.
- Dependent on available published evidence; some emerging modalities lack long-term outcome data.

Introduction

Osteoporosis remains a major global health challenge, with fragility fractures contributing substantially to morbidity, mortality, and healthcare burden [1, 2]. Our review highlights several important developments that have the potential to influence research, clinical practice, and policy. These include the recognition of imminent fracture risk [15], the integration of trabecular bone score and radiofrequency echographic multi-spectrometry into diagnostic pathways [13, 14], and the growing evidence supporting anabolic-first treatment strategies for patients at very high risk [16, 17]. We also discuss the under-recognised impact of vertebral compression fractures on longevity, cardiopulmonary function, and frailty [2, 15].

This narrative review synthesises current knowledge on osteoporosis epidemiology, diagnostic innovations, fracture-risk assessment, and emerging therapeutic strategies, with particular emphasis on anabolic-first sequential therapy [16], bone-quality assessment tools [13, 14], and the clinical role of vitamin D analogues such as alfacalcidol [21].

Osteoporosis is a progressive systemic skeletal disease characterised by reduced bone mass and deterioration of bone microarchitecture, resulting in increased fracture risk [3]. The World Health Organization defines osteoporosis as a T-score ≤ –2.5 at the femoral neck on DXA scanning [6]. Globally, the burden of osteoporosis is rising due to population ageing, with hip fractures associated with a one-year mortality of approximately 20% and significant disability [1, 2].

In the UK alone, fragility fractures number over 527,000 annually and are projected to rise to 665,000 by 2034. The economic burden exceeds £4.5 billion annually [1]. Given the clinical and societal impact, optimising risk assessment and management is a priority [4–6].

Recent literature highlights new risk factors, improved imaging modalities, and evolving therapeutic strategies, including treat-to-target approaches and sequential therapy [5, 12, 16, 20]. This review synthesises these developments.

Osteoporosis is a chronic skeletal disorder characterised by reduced bone strength and increased susceptibility to fragility fractures. With global population ageing, the prevalence and burden of osteoporosis continue to rise. Hip fractures remain particularly devastating, often resulting in loss of independence and increased mortality [1, 2].

Methods

This narrative review draws on peer-reviewed literature identified through a targeted web search. Sources included:

- BMJ clinical review on advances in osteoporosis management
- British Journal of General Practice guidance on primary care management
- Additional contemporary reviews on epidemiology and pharmacological therapy

Inclusion criteria: articles addressing epidemiology, risk factors, diagnostic tools, imaging, fracture risk assessment, and management strategies. Exclusion criteria: studies focused exclusively on paediatric osteoporosis or rare metabolic bone diseases.

Data were extracted and synthesised thematically. This narrative review integrates established clinical knowledge and guideline-based concepts. Themes include epidemiology, risk factors, diagnostic modalities, fracture-risk assessment, and pharmacological and non-pharmacological management. No systematic search or meta-analysis was performed.

Results

Epidemiology and Burden

Osteoporosis predominantly affects older adults, with risk increasing sharply after age 80. Hip fractures carry a 20% one-year mortality and an 86% risk of subsequent fractures within two years. Osteoporosis affects millions worldwide, with prevalence increasing with age. Women are disproportionately affected, particularly post-menopause due to accelerated bone loss.

Risk Factors

Traditional risk factors include age, female sex, low BMI, smoking and alcohol, glucocorticoid use, family history, rheumatoid arthritis and secondary causes (e.g., endocrine disorders, malabsorption). Emerging risk factors include:

- Diabetes mellitus
- Sarcopenia
- Bariatric surgery
- Chronic inflammatory condition

These conditions contribute to skeletal fragility independent of BMD.

Diagnosis and Imaging

DXA remains the gold standard. Recent advances include:

- Trabecular Bone Score (TBS): assesses bone microarchitecture

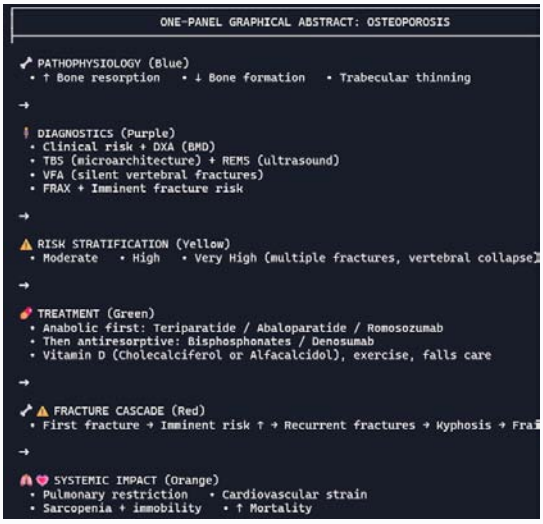

Figure 1: Graphical Summary: Integrated Model of Osteoporosis Risk, Diagnosis, and Treatment Pathways.
This graphical summary illustrates the contemporary framework for osteoporosis care. The left panel depicts major contributors to skeletal fragility, including age-related bone loss, secondary causes (endocrine, renal, inflammatory), lifestyle factors, and the impact of vertebral compression fractures on morbidity and mortality. The central panel outlines the diagnostic pathway, beginning with clinical risk assessment and progressing through DXA, TBS, REMS, and vertebral fracture assessment to determine fracture probability and imminent risk. The right panel summarises therapeutic strategies, highlighting the shift toward risk-stratified management, the role of vitamin D analogues such as alfacalcidol, and the sequential therapy model in which anabolic agents (teriparatide, abaloparatide, romosozumab) are followed by antiresorptives to consolidate gains. The bottom section emphasises the consequences of untreated osteoporosis, including recurrent fractures, kyphosis, frailty, cardiopulmonary compromise, and reduced longevity.

- Radiofrequency Echographic Multi-Spectrometry (REMS): radiation-free modality with potential use in specific populations

Diagnostic Advances

1. DXA (Dual-Energy X-ray Absorptiometry)

Still the gold standard for BMD measurement.

2. Trabecular Bone Score (TBS)

Provides insight into bone microarchitecture independent of BMD.

3. Radiofrequency Echographic Multi-Spectrometry (REMS)

A radiation-free ultrasound-based modality with growing clinical interest.

4. Vertebral Fracture Assessment (VFA)

Allows detection of asymptomatic vertebral fractures during DXA.

Fracture Risk Assessment

The shift from BMD-based diagnosis to fracture-risk–based treatment is well established. Tools include:

- FRAX: widely used for 10-year fracture risk
- FRAXplus: incorporates additional risk factors for refined stratification

Risk-based assessment integrates:

- BMD
- Clinical risk factors
- Prior fractures
- Glucocorticoid exposure
- Falls risk

Management

Non-pharmacological

- Fall prevention strategies
- Resistance and balance training
- Adequate calcium and vitamin D supplementation
- Possible role for vitamin K
- Fracture liaison services to close care gaps
- Weight-bearing and resistance exercise
- Smoking cessation and alcohol moderation

Pharmacological

A major shift is the emphasis on sequential therapy:

- Anabolic agents first (e.g., teriparatide, romosozumab) for highest-risk patients
- Followed by antiresorptives (bisphosphonates, denosumab) to maintain gains

This contrasts with the traditional step-up approach.

1. Vitamin D Analogues: Alfacalcidol

Alfacalcidol is a synthetic analogue converted to active calcitriol in the liver.

Roles include:

- Improving calcium absorption
- Supporting bone mineralisation
- Beneficial in elderly patients with impaired renal activation of vitamin D
- Sometimes used in combination with antiresorptives

2. Antiresorptive Agents

- Bisphosphonates (alendronate, risedronate, zoledronate)
- Denosumab

These reduce bone turnover and fracture risk.

3. Anabolic Therapies (PTH Analogues)

- Teriparatide (PTH 1-34)
- Abaloparatide (PTHrP analogue)

Mechanism: Stimulate osteoblast activity, increasing bone formation.

Indications: Severe osteoporosis, multiple fractures, very high fracture risk.

Table 1. Comprehensive Risk Factors for Osteoporosis and Fragility Fractures

Category	Risk Factors
Demographic	Age, female sex, low BMI
Lifestyle	Smoking, alcohol, inactivity
Medical	RA, diabetes, hyperthyroidism
Medications	Steroids, AIs, ADT
Nutritional	Vitamin D deficiency
Secondary	Bariatric surgery, CKD
Fracture-related	Prior fracture, falls

Table 1: Comprehensive Risk Factors for Osteoporosis and Fragility Fractures.
This table summarises the major demographic, lifestyle, medical, nutritional, medication-related, and fracture-related factors that contribute to osteoporosis and fragility fracture risk. It highlights the multifactorial nature of skeletal fragility and the importance of integrating clinical risk factors with bone mineral density in routine assessment.

Table 2. Secondary Causes of Osteoporosis

Category	Examples
Endocrine	Hyperthyroidism, Cushing's
GI	Coeliac disease, IBD
Renal	CKD
Hematologic	Myeloma
Rheumatologic	RA, SLE
Nutritional	Malnutrition
Medications	Steroids, PPIs

Table 2: Secondary Causes of Osteoporosis.
This table outlines key secondary contributors to osteoporosis across endocrine, gastrointestinal, renal, haematologic, rheumatologic, nutritional, and medication-related categories. It emphasises the need for targeted evaluation to identify reversible or treatable underlying conditions that may accelerate bone loss.

4. Sclerostin Inhibitor

- Romosozumab

Dual action: increases bone formation and decreases resorption.

Used for one year followed by antiresorptive therapy.

Expanded Recent Advances

The field of osteoporosis has undergone rapid evolution. Key advances include:

1. Imminent Fracture Risk Recognition

Patients with a recent fracture have a dramatically elevated risk of another fracture within 12–24 months. This has shifted guidelines toward urgent initiation of therapy, often with anabolic agents.

2. Sequential Therapy as Standard of Care

Evidence now supports:

- Anabolic first → rapid BMD gains
- Antiresorptive second → long-term consolidation

This approach reduces early fractures and improves long-term outcomes.

Table 3. Imaging Modalities in Osteoporosis

Modality	Measures	Strengths	Limitations
DXA	BMD	Standardised	No bone quality
TBS	Microarchitecture	Adds risk info	Not diagnostic alone
REMS	Bone status	No radiation	Limited long-term data
VFA	Vertebral fractures	Detects silent fractures	Variable quality

Table 3: Imaging Modalities in Osteoporosis.
This table compares commonly used imaging tools—DXA, trabecular bone score, radiofrequency echographic multi-spectrometry, and vertebral fracture assessment—highlighting what each modality measures, its strengths, and its limitations. It illustrates how combining bone density with bone quality and vertebral imaging improves diagnostic accuracy.

Dedicated Section: Alfacalcidol vs. Cholecalciferol

Feature	Alfacalcidol	Cholecalciferol
Activation	Liver only	Liver + kidney
CKD use	Effective	Less effective
Hypercalcaemia	Higher risk	Lower risk
Role	Adjunct	Standard replacement

Anabolic Therapies

Table 4. Comparison of Anabolic Agents

Feature	Teriparatide	Abaloparatide	Romosozumab
Class	PTH analogue	PTHrP analogue	Sclerostin inhibitor
Mechanism	↑ Formation	↑ Formation	↑ Formation + ↓ Resorption
Duration	24 mo	18 mo	12 mo
Best For	Severe OP	Very high risk	Severe OP
Sequential	Required	Required	Required

Table 4: Comparison of Anabolic Agents.
This table provides a side-by-side comparison of teriparatide, abaloparatide, and romosozumab, including their mechanisms of action, duration of therapy, clinical indications, and role within sequential treatment pathways. It supports evidence-based selection of anabolic therapy for patients at very high fracture risk.

3. Novel Imaging and Digital Tools

- REMS for radiation-free assessment
- TBS for microarchitecture
- AI-enhanced fracture prediction models
- Digital health tools for adherence monitoring

4. New Therapeutic Targets

Research is exploring:

- Senolytics (targeting senescent osteocytes)
- Cathepsin K inhibitors
- Wnt pathway modulators

Table 5. Sequential Therapy Pathways

Risk Category	First-Line	Follow-Up
Very High	Anabolic	Antiresorptive
High	Antiresorptive	Long-term antiresorptive
Moderate	Lifestyle ± bisphosphonate	Reassess

Table 5: Sequential Therapy Pathways.
This table outlines recommended treatment sequences for moderate-, high-, and very high-risk patients. It illustrates the anabolic-first approach for very high-risk individuals, followed by antiresorptive consolidation, and contrasts this with standard antiresorptive-first strategies for lower-risk groups.

- Combination anabolic–antiresorptive regimens

5. Personalised Medicine Approaches

Risk stratification now incorporates:

- Bone quality
- Fall risk
- Comorbidities
- Renal function
- Patient preference

This supports more tailored therapy selection.

6. Treat-to-Target Approaches

Targets include:

- Achieving T-score above a threshold
- Reducing imminent fracture risk
- Improving bone quality metrics (e.g., TBS)

7. Future Therapies

Research into senolytics and senomorphics suggests potential to address cellular senescence and age-related bone loss.

Discussion

This review highlights the evolving landscape of osteoporosis management. The recognition of new risk factors such as diabetes and sarcopenia underscores the need for broader clinical assessment beyond BMD [1, 3, 11]. Tools like FRAXplus improve risk stratification, enabling more personalised care [5].

Advances in imaging, including TBS and REMS, offer insights into bone quality, though their integration into routine practice requires further validation [13, 14]. The shift toward fracture-risk–based treatment aligns with evidence that BMD alone underestimates risk in many patients [5, 12, 15].

Sequential therapy represents a paradigm shift, particularly for those at highest risk. Starting with anabolic agents may reduce early fracture risk more effectively than traditional approaches [16, 17]. However, cost, access, and long-term data remain challenges [2, 18].

Non-pharmacological strategies and fracture liaison services remain essential components of comprehensive care [1, 4].

Osteoporosis management has evolved from a BMD-centric

Table 6. Pharmacological Therapies in Osteoporosis

Drug Class	Examples	Mechanism of Action	Clinical Use / Indications	Key Considerations
Bisphosphonates	Alendronate, Risedronate, Ibandronate, Zoledronate	Inhibit osteoclast-mediated bone resorption	First-line for moderate–high risk; prevention and treatment of vertebral and non-vertebral fractures	Oral intolerance; contraindicated in severe renal impairment; rare risk of ONJ and AFF
RANKL Inhibitor	Denosumab	Monoclonal antibody blocking RANKL → prevents osteoclast formation	High risk patients; alternative when bisphosphonates unsuitable	Requires continuous dosing; rebound bone loss if stopped without consolidation therapy
Anabolic Agents (PTH/PTHrP analogues)	Teriparatide, Abaloparatide	Stimulate osteoblast activity → increase bone formation	Very high-risk patients; multiple fractures; vertebral collapse	Limited duration (24 months); follow with antiresorptive therapy
Sclerostin Inhibitor	Romosozumab	Dual effect: ↑ bone formation + ↓ resorption	Very high-risk patients, especially with vertebral fractures	Avoid in patients with recent MI or stroke; follow with antiresorptive therapy
Selective Estrogen Receptor Modulator (SERM)	Raloxifene	Estrogen agonist in bone → reduces resorption	Vertebral fracture prevention in postmenopausal women	Risk of VTE; no benefit for hip fracture
Hormone Therapy	Estrogen, Estrogen–Progestin	Reduces bone turnover	Early postmenopausal women with menopausal symptoms	Not first-line solely for osteoporosis; cardiovascular and cancer risks
Vitamin D Analogues	Cholecalciferol, Alfacalcidol	Improve calcium absorption; alfacalcidol bypasses renal activation	Deficiency correction; alfacalcidol useful in CKD, frailty	Monitor calcium; essential adjunct to all therapies
Calcitonin	Salmon calcitonin	Inhibits osteoclast activity	Limited role; short-term pain relief in acute vertebral fractures	Not recommended for long-term fracture prevention

Table 6: Pharmacological Therapies in Osteoporosis.
This table summarises the major pharmacological options for osteoporosis, including antiresorptive agents, anabolic therapies, hormone-based treatments, and vitamin D analogues. For each drug class, the table outlines representative agents, mechanisms of action, clinical indications, and key considerations relevant to safety, sequencing, and patient selection. It highlights the central role of anabolic-first therapy in very high-risk patients, the importance of antiresorptive consolidation, and the specific utility of alfacalcidol in individuals with renal impairment or frailty.

Table 7. Non-pharmacological Therapies in Osteoporosis

Therapy Category	Examples / Components	Mechanism / Rationale	Clinical Impact
Nutrition	Adequate calcium intake; vitamin D optimisation; protein-rich diet	Supports bone mineralisation; improves muscle mass and function	Reduces fracture risk; improves response to pharmacotherapy
Exercise & Physical Activity	Weight-bearing exercise; resistance training; balance and gait training	Stimulates bone formation; improves muscle strength and proprioception	Reduces falls; increases BMD modestly; improves mobility
Fall-Prevention Strategies	Home hazard assessment; footwear optimisation; vision correction; medication review	Reduces environmental and physiological fall risks	Lowers incidence of fall-related fractures
Lifestyle Modification	Smoking cessation; alcohol moderation; maintaining healthy body weight	Reduces bone loss and improves overall metabolic health	Slows progression of osteoporosis; reduces fracture risk
Hip Protectors	Padded garments for frail or institutionalised adults	Absorb impact energy during falls	Reduces hip fracture risk in high-risk populations
Posture & Spinal Care	Back-strengthening exercises; posture training; spinal orthoses (select cases)	Improves spinal alignment; reduces kyphosis progression	Reduces pain; improves function in vertebral fracture patients
Multidisciplinary Rehabilitation	Physiotherapy; occupational therapy; frailty assessment	Addresses sarcopenia, balance, mobility, and functional decline	Enhances independence; reduces recurrent fractures
Sunlight Exposure	Safe, regular outdoor exposure	Enhances endogenous vitamin D synthesis	Supports bone health and muscle function

Table 7: Non-pharmacological Therapies in Osteoporosis.
This table summarises key non-pharmacological strategies that complement medical therapy in osteoporosis management. It includes nutritional optimisation, structured exercise programmes, fall-prevention measures, lifestyle modification, hip protectors, posture and spinal care, multidisciplinary rehabilitation, and safe sunlight exposure. These interventions play a critical role in reducing falls, improving musculoskeletal function, enhancing quality of life, and supporting the effectiveness of pharmacological treatments.

model to a more nuanced, risk-based approach. Diagnostic innovations such as TBS and REMS provide complementary insights into bone quality, while vertebral fracture assessment improves detection of silent fractures [13, 14, 12].

Therapeutically, the landscape has expanded significantly. Antiresorptives remain foundational, but anabolic agents and romosozumab offer powerful options for high-risk patients [16, 17, 18]. The role of alfacalcidol is particularly relevant in older adults and those with impaired vitamin D activation [21-23].

Sequential therapy represents a major paradigm shift, emphasising early, aggressive treatment for those at highest risk [16]. This aligns with the concept of "imminent fracture risk," recognising that recent fractures predict near-term recurrence [15].

Table 8. Treatment Selection by Phenotype

Patient Phenotype	Key Characteristics	Preferred First-Line Therapy	Sequencing Strategy	Additional Considerations
Very High Fracture Risk	Multiple fragility fractures; vertebral collapse; very low BMD; high imminent risk	**Anabolic therapy** (teriparatide, abaloparatide, romosozumab)	Follow with antiresorptive (bisphosphonate or denosumab)	Early VFA; fall-risk assessment; vitamin D optimisation
Single Vertebral Fracture	Recent or silent vertebral fracture; moderate–high risk	**Anabolic therapy** preferred; antiresorptive acceptable if access limited	Consolidate with antiresorptive	Consider REMS/TBS to assess microarchitecture
Glucocorticoid-Induced Osteoporosis	Chronic steroid use; rapid bone loss	**Anabolic therapy** or denosumab	Anti-resorptive consolidation after anabolic phase	Monitor vitamin D; minimise steroid dose
Postmenopausal Women with High FRAX but No Fractures	High 10-year fracture probability; osteopenia or osteoporosis	**Bisphosphonate** (oral or IV)	Long-term antiresorptive; consider anabolic if risk escalates	Lifestyle optimisation; fall-prevention
Renal Impairment (CKD 3–4)	Reduced renal activation of vitamin D; limited bisphosphonate use	**Denosumab**; **alfacalcidol** for vitamin D strategy	Continue denosumab long-term; avoid abrupt cessation	Monitor calcium; avoid bisphosphonates in advanced CKD
Frailty / Sarcopenia	Low muscle mass; high fall risk; poor mobility	**Anabolic therapy** preferred	Anti-resorptive consolidation	Physiotherapy; protein intake; hip protectors
Younger Postmenopausal Women (<65) with Low BMD	Early menopause; accelerated bone loss	**Bisphosphonate** or **SERM** depending on fracture pattern	Continue antiresorptive; reassess at menopause transition	Consider HRT if symptomatic and appropriate
Men with Osteoporosis	Hypogonadism; secondary causes common	**Bisphosphonate** or **denosumab**	Consolidation with antiresorptive	Evaluate testosterone; screen for secondary causes
Patients Unable to Tolerate Oral Therapy	GI intolerance; adherence challenges	**IV zoledronate** or **denosumab**	Maintain long-term antiresorptive	Annual infusion improves adherence

Table 8: Treatment Selection by Phenotype.
This table presents a phenotype-based approach to osteoporosis management, aligning specific patient profiles with optimal therapeutic strategies. It highlights the role of anabolic-first therapy in very high-risk individuals, the use of denosumab in renal impairment or oral intolerance, and the importance of tailored vitamin D strategies such as alfacalcidol in frailty and chronic kidney disease. The table supports personalised, risk-aligned treatment decisions that integrate fracture history, comorbidities, bone quality, and imminent fracture risk.

Despite advances, challenges remain: underdiagnosis, undertreatment, limited access to anabolic therapies and the need for long-term outcome data on newer modalities [1, 2, 18].

Table 9. Secondary Fracture Prevention Pathway

Step	Components	Purpose / Rationale
1. Identification of Index Fragility Fracture	Hip, vertebral, wrist, humerus, pelvis, rib fractures (clinical or radiographic)	Early recognition triggers secondary prevention; vertebral fractures often silent and require VFA
2. Immediate Post-Fracture Assessment (within 2–12 weeks)	Clinical risk assessment; medication review; falls history; pain and mobility evaluation	Identifies reversible risks and urgent needs; establishes baseline for treatment
3. Fracture Liaison Service (FLS) Coordination	Automatic referral; nurse-led assessment; multidisciplinary input	Ensures systematic, standardised secondary prevention and reduces care gaps
4. Diagnostic Work-Up	DXA (BMD); TBS; REMS (if available); VFA; labs for secondary causes (calcium, vitamin D, renal, thyroid, PTH)	Confirms osteoporosis, identifies microarchitectural deterioration, and detects secondary contributors
5. Risk Stratification	Moderate, high, or very high risk; imminent fracture risk assessment	Guides therapy selection, especially anabolic-first strategies for very high-risk patients
6. Initiation of Pharmacotherapy	Anabolic therapy for very high risk; antiresorptive therapy for high/moderate risk; vitamin D optimisation	Reduces risk of subsequent fractures; early treatment is critical within the imminent risk window
7. Falls and Frailty Management	Balance training; physiotherapy; home hazard assessment; vision correction; hip protectors in frailty	Reduces fall-related fractures; addresses sarcopenia and mobility decline
8. Lifestyle and Nutritional Optimisation	Adequate calcium and protein intake; vitamin D; smoking cessation; alcohol moderation	Supports bone health and enhances treatment response
9. Follow-Up and Monitoring	Review at 3–6 months, then annually; adherence checks; repeat DXA/TBS every 1–2 years	Ensures treatment persistence, evaluates response, and adjusts therapy as needed
10. Long-Term Maintenance	Continued antiresorptive therapy; reassessment after anabolic phase; ongoing fall-prevention	Maintains bone strength and reduces long-term fracture risk

Table 9: Secondary Fracture Prevention Pathway.
This table outlines a structured, evidence-based pathway for secondary fracture prevention following an initial fragility fracture. It emphasises early identification, coordinated care through fracture liaison services, comprehensive diagnostic evaluation, risk-aligned pharmacotherapy, fall-prevention strategies, nutritional optimisation, and long-term monitoring. The pathway is designed to reduce recurrent fractures, address imminent fracture risk, and improve functional outcomes in older adults.

Historically, osteoporosis management relied heavily on bone mineral density (BMD) thresholds. However, BMD alone does not fully capture fracture risk. Over the past decade, the field has shifted toward fracture-risk–based assessment, incorporating clinical risk factors, bone quality metrics, and dynamic prediction tools [5, 12, 13].

Therapeutic options have expanded significantly. Traditional antiresorptives remain foundational, but anabolic agents, vitamin D analogues such as alfacalcidol, and novel biologics have reshaped treatment strategies [16, 17, 21]. Sequential therapy — beginning with an anabolic agent followed by an antiresorptive — is increasingly recognised as optimal for high-risk individuals [16, 20].

This review synthesises these developments, offering a contemporary overview suitable for clinicians, educators, and researchers.

A personalised, holistic approach integrating risk assessment, lifestyle interventions, and tailored pharmacotherapy is essential [1, 4, 6].

Despite advances, challenges remain:

- Underdiagnosis
- Undertreatment
- Limited access to anabolic therapies
- Need for long-term outcome data on newer modalities

A personalised, holistic approach integrating risk assessment, lifestyle interventions, and tailored pharmacotherapy is essential.

How this study might affect research, practice, or policy

This review highlights several areas where contemporary understanding of osteoporosis can meaningfully influence future research directions, clinical practice, and health policy.

Implications for Research

- Shift toward bone quality and microarchitecture: The growing use of TBS and REMS underscores the need for studies that evaluate how bone quality metrics predict fractures independently of BMD.
- Evaluation of sequential therapy: Evidence supporting anabolic-first strategies calls for long-term comparative trials to determine optimal sequencing, duration, and cost-effectiveness.
- Understanding imminent fracture risk: Research is needed to clarify biological mechanisms behind the sharply elevated risk following a recent fracture and to identify biomarkers that predict early refracture.
- Vitamin D analogues in special populations: The distinct role of alfacalcidol in older adults and those with renal impairment warrants targeted trials comparing it with cholecalciferol in fracture prevention.
- Impact of vertebral fractures on longevity: The strong association between vertebral compression fractures, frailty, and mortality highlights the need for mechanistic studies exploring cardiopulmonary compromise, sarcopenia, and systemic inflammation.

Implications for Clinical Practice

- Earlier identification of high-risk patients: Incorporating VFA, TBS, and REMS into routine assessment may allow clinicians to detect silent vertebral fractures and microarchitectural deterioration earlier.
- Risk-based treatment selection: Clinicians may increasingly adopt fracture-risk–based pathways rather than relying solely on BMD thresholds, enabling more personalised therapy.
- Greater use of anabolic agents: Recognition of the benefits

of anabolic-first therapy in very high-risk patients may shift prescribing patterns, particularly for those with multiple fractures or vertebral collapse.

- Optimised vitamin D strategies: Differentiating between alfacalcidol and cholecalciferol may improve management in elderly or renally impaired patients, reducing falls and fracture risk.
- Holistic management of vertebral fractures: Understanding the profound morbidity and mortality associated with vertebral compression fractures may encourage more aggressive pain management, rehabilitation, and fall-prevention strategies.

Implications for Policy

- Prioritising fracture liaison services (FLS): Given the high imminent fracture risk after a first fragility fracture, expanding FLS coverage could significantly reduce secondary fractures and healthcare costs.
- Improved access to advanced imaging: Policies supporting reimbursement for TBS, REMS, and VFA could enhance early detection and risk stratification.
- Funding for anabolic therapies: As evidence grows for sequential therapy, policymakers may need to reconsider cost-effectiveness models to improve access for high-risk patients.
- Public health strategies for ageing populations: Recognising the long-term mortality impact of vertebral fractures may prompt national initiatives focused on fall prevention, vitamin D optimisation, and early screening.
- Integration of osteoporosis into chronic disease frameworks: Given its systemic consequences and impact on longevity, osteoporosis may warrant inclusion in broader frailty and multimorbidity policies.

Gaps in Current Practice

Despite significant advances in diagnostic technologies, therapeutic options, and risk-stratification strategies, substantial gaps persist in the real-world management of osteoporosis. These gaps contribute to missed diagnoses, delayed treatment, recurrent fractures, and preventable morbidity and mortality.

1. Under-diagnosis of Vertebral Fractures

Vertebral compression fractures are frequently missed in routine care because:

- Many are asymptomatic or present with non-specific back pain
- Vertebral Fracture Assessment (VFA) is not routinely performed during DXA
- Clinicians often underestimate the prognostic significance of vertebral deformities

This leads to failure to identify patients at very high or imminent fracture risk, delaying appropriate intervention.

2. Over-reliance on BMD Thresholds

Clinical decisions often hinge solely on DXA-derived T-scores, despite clear evidence that:

- Many fragility fractures occur in individuals with osteopenia
- Bone quality (microarchitecture) is not captured by BMD
- Clinical risk factors can outweigh BMD in predicting fractures

This narrow focus results in under-treatment of high-risk individuals with "normal" or "borderline" BMD.

3. Limited Integration of Advanced Imaging

Although tools such as TBS and REMS provide valuable insights into bone quality:

- Access remains inconsistent
- Reimbursement pathways are unclear
- Clinician familiarity is variable
- These modalities are not yet embedded in standard care pathways

As a result, opportunities to refine risk assessment are often missed.

4. Suboptimal Use of Anabolic and Sequential Therapy

Despite strong evidence supporting anabolic-first strategies for very high-risk patients:

- Bisphosphonates remain the default first-line therapy
- Access to anabolic agents is limited by cost and prescribing restrictions
- Clinicians may lack confidence or experience with newer agents
- Sequential therapy pathways are not consistently implemented

This contributes to inadequate fracture prevention in the highest-risk groups.

5. Inadequate Vitamin D Strategy in High-Risk Populations

Vitamin D supplementation is common, but differentiation between:

- Cholecalciferol (general replacement)
- Alfacalcidol (useful in renal impairment, frailty, and impaired activation states)
- is often overlooked. This leads to:
- Persistent deficiency in vulnerable populations
- Suboptimal calcium absorption
- Increased falls and fracture risk

6. Fragmented Post-Fracture Care

Secondary fracture prevention remains inconsistent due to:

- Limited availability of fracture liaison services (FLS)
- Poor communication between acute care and primary care
- Lack of systematic follow-up after vertebral or non-hip fractures

Consequently, many patients experience preventable second fractures.

7. Insufficient Focus on Frailty, Sarcopenia, and Multimorbidity

Osteoporosis is often managed in isolation, despite strong interactions with:

- Muscle weakness
- Balance impairment
- Chronic inflammation
- Cardiopulmonary compromise after vertebral fractures

This siloed approach misses opportunities for integrated, geriatric-oriented care.

8. Underestimation of Mortality Risk

Clinicians often underestimate the profound impact of vertebral fractures on longevity. Key issues include:

- Lack of awareness of the increased all-cause mortality associated with multiple fractures
- Under-recognition of cardiopulmonary compromise from kyphosis
- Failure to appreciate the rapid decline in physiological reserve following vertebral collapse

9. Poor Patient Engagement and Adherence

Patients frequently lack understanding of:

- Their fracture risk
- The chronic nature of osteoporosis
- The importance of long-term therapy adherence
- Lifestyle and fall-prevention strategies

This contributes to high rates of treatment discontinuation.

10. Policy and System-Level Barriers

Healthcare systems often lack:

- Universal access to advanced imaging
- Funding models that support anabolic therapy
- National screening strategies for high-risk populations
- Integrated fracture-prevention pathways

These systemic gaps perpetuate inequities in osteoporosis care.

Expanded Section: Morbidity, Mortality, and Longevity Impact of Vertebral Compression Fractures and Multiple Fragility Fractures

Vertebral compression fractures (VCFs) are among the most clinically significant manifestations of osteoporosis. Although often underdiagnosed, they carry profound consequences for morbidity, mortality, and long-term functional independence.

1. Morbidity Associated with Vertebral Compression Fractures

Pain and Functional Decline

VCFs frequently cause acute and chronic pain, leading to:

- Reduced mobility
- Impaired ability to perform activities of daily living
- Increased dependence on caregivers
- Higher risk of institutionalisation

Chronic pain may persist even after radiographic healing due to altered spinal biomechanics and paraspinal muscle fatigue**.**

Kyphosis and Postural Changes

Progressive vertebral collapse leads to:

- Thoracic kyphosis
- Loss of height
- Impaired balance
- Increased falls risk
- Restrictive lung disease due to reduced thoracic volume

Psychological Impact

Patients often experience:

- Depression
- Social withdrawal
- Fear of falling
- Reduced quality of life

2. Mortality Risk and Longevity Impact

Increased Mortality After Vertebral Fractures

Multiple studies demonstrate that vertebral fractures are associated with significantly increased mortality, independent of age and comorbidities. Contributing factors include:

- Immobility-related complications (pneumonia, thromboembolism)
- Chronic pain leading to reduced physical activity
- Frailty and sarcopenia
- Increased risk of subsequent fractures

Imminent Fracture Risk

A vertebral fracture increases the risk of another fracture within 1–2 years, creating a cycle of:

- Recurrent fractures
- Progressive deformity
- Declining physiological reserve

This “fracture cascade” is a major driver of reduced longevity.

Multiple Fragility Fractures and Survival

Patients with two or more fragility fractures have:

- Higher all-cause mortality
- Greater disability
- Increased hospitalisation rates
- Accelerated decline in independence

Hip fractures combined with vertebral fractures carry the highest mortality, often exceeding that of many chronic diseases.

3. Mechanisms Linking Vertebral Fractures to Reduced Longevity

Respiratory Compromise

Kyphosis reduces lung capacity, predisposing to:

- Recurrent respiratory infections
- Hypoventilation
- Reduced exercise tolerance

Cardiovascular Effects

Severe kyphosis alters thoracic cavity geometry, potentially affecting:

- Cardiac output
- Venous return
- Autonomic balance

Frailty and Sarcopenia

Pain-induced inactivity accelerates:

- Muscle loss
- Balance impairment
- Falls risk

Chronic Systemic Inflammation

Bone microdamage and immobility contribute to:

- Low-grade inflammation
- Catabolic hormonal changes
- Reduced anabolic response

4. Clinical Implications

Early Identification

Silent vertebral fractures detected via VFA or imaging should trigger:

- Reclassification to high or very high fracture risk
- Consideration of anabolic therapy
- Aggressive fall-prevention strategies

Therapeutic Urgency

Patients with vertebral fractures benefit most from:

- Early initiation of anabolic therapy
- Sequential antiresorptive therapy
- Optimisation of vitamin D (including alfacalcidol in selected patients)

Holistic Management

Addressing pain, mobility, nutrition, and psychological wellbeing is essential to improving survival and quality of life.

Conclusion

Osteoporosis continues to impose substantial clinical and economic burdens. Recent advances in risk assessment, imaging, and pharmacological therapy offer opportunities for more precise and effective management. A personalised, goal-directed approach—integrating fracture risk, patient characteristics, and sequential therapy—represents the future of osteoporosis care. Continued research into novel therapeutics and implementation strategies will be essential to reduce the global burden of fragility fractures. Osteoporosis continues to impose a substantial global burden. Advances in diagnostic tools, risk-stratification strategies, and therapeutic options — including alfacalcidol, PTH analogues, and romosozumab — have transformed management. A personalised, sequential, and risk-based approach offers the best opportunity to reduce fractures and improve quality of life.

Funding and Ethics/Compliance Statements Block

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests

The authors declare that they have no competing interests.

Ethics Approval

Not applicable. This study is a narrative review of published literature and did not involve human participants or animal subjects.

Patient and Public Involvement

No patients or members of the public were directly involved in the design, conduct, reporting, or dissemination of this review.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Author Contributions

All authors conceived the study. conducted the literature search and drafted the manuscript. All authors contributed to revisions, approved the final version, and agree to be accountable for all aspects of the work.

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