OSTEOPOROSIS

AN EXPLODING PROBLEM OF THE AGING POPULATION

APRNworld

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ANCC Accredited NCPD Hours: 2 hrs

Target Audience: RN/APRN

NEED ASSESSMENT

Osteoporosis is a chronic bone disorder characterized by significant alterations in bone microarchitecture and a reduction in bone mineral density (BMD). It leads to compromised bone strength and increased susceptibility to fractures. It affects millions globally across diverse ethnic populations and poses a particularly significant health burden among the elderly, a rapidly expanding demographic worldwide.

This condition results from an imbalance between bone resorption and bone formation, leading to progressive deterioration of bone tissue. The consequent loss of bone mass and structural integrity impairs the bone's ability to withstand mechanical stress, substantially increasing the risk of fragility fractures, particularly in the hip, spine, and wrist.

Bone fragility represents the most serious clinical outcome of osteoporosis and necessitates long-term medical management and lifestyle modifications, especially in older adults. The clinical impact of fractures in this population includes increased morbidity, reduced quality of life, and elevated mortality risk.

Osteoporosis is a multifactorial disease influenced by both genetic predispositions and environmental factors. Numerous genes involved in bone metabolism, such as those encoding for collagen type I, vitamin D receptor, and oestrogen receptor, have been identified as contributors to disease susceptibility. These genetic markers hold promise as early diagnostic biomarkers, particularly for individuals with a family history of osteoporosis, facilitating timely intervention and risk reduction strategies.

OBJECTIVES

- **Define osteoporosis** and explain its pathophysiology using standard clinical terminology.
- **Differentiate between the two major types of primary osteoporosis** (including their aetiology, age of onset, and common fracture sites.
- **Discuss the epidemiological impact of osteoporosis** concerning global prevalence, population at risk, economic burden, and public health implications.
- **Identify at least six key risk factors and causes of osteoporosis**, and discuss the diagnostic criteria and various diagnostic tests used.
- **Discuss the management criteria for osteoporosis based on underlying medical conditions and elaborate on the pharmacologic agents** used.

GOAL

The purpose of this article is to provide a comprehensive review of osteoporosis, focusing on its pathophysiology and aetiology, current strategies for screening and diagnosis, and an evaluation of selected clinical guidelines and professional recommendations. Additionally, the article explores evidence-based approaches to nonpharmacological and pharmacological management, with particular attention to the efficacy, safety, and cost-effectiveness of available therapeutic options.

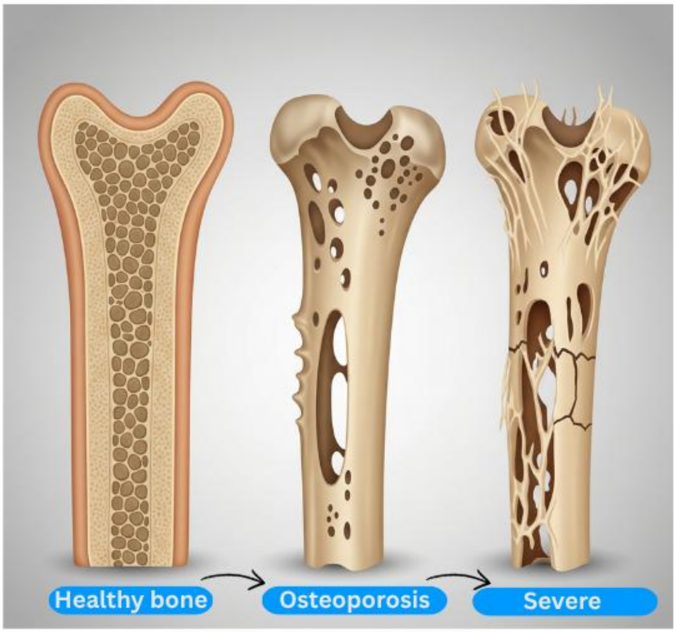
INTRODUCTION

Osteoporosis is a chronic metabolic bone disorder affecting approximately 10 million men and women in the United States. It is characterized by decreased bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to an increased risk of fragility fractures. These fractures are associated with significant clinical and economic burdens, including chronic pain, loss of mobility, disability, increased rates of nursing home placement, elevated healthcare costs, and higher mortality. Diagnosis is primarily established through non-invasive dual-energy X-ray absorptiometry (DXA), the gold standard for assessing BMD. Pharmacologic interventions include bisphosphonates, oestrogen receptor agonists/antagonists, parathyroid hormone analogues, and calcitonin. Emerging therapies with novel mechanisms, such as cathepsin K inhibitors and monoclonal antibodies targeting sclerostin, represent promising advancements in treating high-risk or treatment-resistant osteoporosis.

OSTEOPOROSIS

Definition

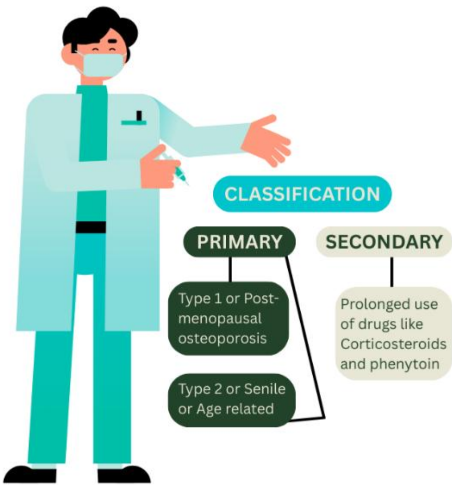
Osteoporosis is a chronic, systemic skeletal disease marked by decreased bone mass, compromised bone tissue integrity, and alterations in bone macro- and microarchitecture, material properties, and geometry, coupled with accumulated micro-damage. These changes weaken bone strength, significantly elevating fracture risk, particularly in the hip, spine, and wrist, often with minimal trauma. The condition is typically progressive, influenced by aging, hormonal changes, genetic factors, and lifestyle, and is diagnosed via bone mineral density (BMD) assessment, commonly using dual-energy X-ray absorptiometry (DXA).



Osteoporosis is broadly divided into two main categories based on aetiology:

Primary Osteoporosis:

- Encompasses age- and sex-related forms, including:
  - **Juvenile Osteoporosis**:
    Rare, occurring in children or adolescents, often idiopathic, with impaired bone development.
  - **Postmenopausal Osteoporosis**:
    Driven by oestrogen deficiency in women post-menopause, accelerating bone resorption and loss.
  - **Male Osteoporosis**:
    Less common, often linked to age-related testosterone decline, genetic factors, or lifestyle.
  - **Senile Osteoporosis**:
    Age-related, affecting both sexes, resulting from cumulative bone loss and impaired bone formation in older age.
- Primarily influenced by aging, hormonal changes (e.g., estrogen or testosterone deficiency), genetic predisposition, and lifestyle factors (e.g., inadequate calcium/vitamin D, physical inactivity).



Secondary Osteoporosis:

- Results from underlying medical conditions or external factors, including:
  - **Diseases**:
    Endocrine disorders (e.g., hyperthyroidism, hyperparathyroidism, hypogonadism), gastrointestinal conditi - ons (e.g., celiac disease, inflammatory bowel disease), hematologic disord- ers(e.g., multiple myeloma), or connect- ive tissue diseases (e.g., rheumatoid arthritis).
  - **Medications**:
    Prolonged use of gluco corticoids (e.g., prednisone), anticonvulsants (e.g., phenytoin), proton pump inhibitors, or certain cancer therapies (e.g., aromatase inhibitors).
- Characterized by accelerated bone loss or impaired bone formation secondary to the primary condition or treatment, often compounding age-related bone decline.

This classification aids in tailoring diagnostic and therapeutic approaches. Primary osteoporosis is often managed through lifestyle interventions and antiresorptive therapies, while secondary osteoporosis requires addressing the underlying cause alongside bone-specific treatments.

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Osteoporosis arises from an imbalance in bone remodelling, where bone resorption by osteoclasts outpaces bone formation by osteoblasts, leading to reduced bone mass, deteriorated microarchitecture, and increased fracture risk. This disruption is driven by multiple interconnected factors, detailed below.

1. Imbalance in Bone Remodelling

- **Core Mechanism**:
  Bone remodelling involves a dynamic balance between osteoclastic bone resorption and osteoblastic bone formation. In osteoporosis, resorption exceeds formation, resulting in net bone loss and compromised structural integrity.
- **Consequences**:
  Loss of trabecular and cortical bone density, thinning of bone trabeculae, and increased porosity weaken bones, predisposing them to fragility fractures.

2. Increased Osteoclastic Activity

- **Mechanism**:
  Osteoclasts, activated by signalling pathways (e.g., RANKL/RANK), excessively break down bone matrix, releasing calcium and degrading structural components.
- **Triggers**:
  - **Hormonal Changes**:

Oestrogen deficiency (e.g., post menopause) upregulates RANKL, enhancing osteoclast activity and survival.

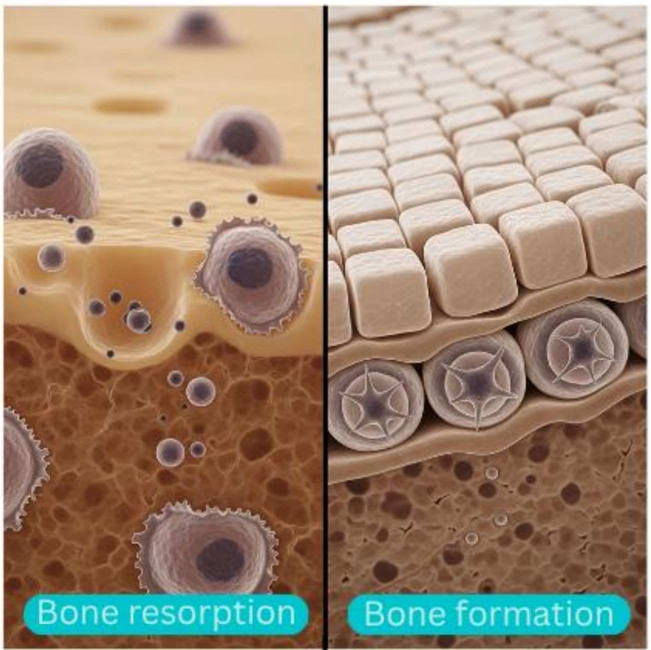
- **Cytokine Dysregulation**:
  Pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) in aging or chronic diseases amplify osteoclast genesis.

- **Impact**:
  Accelerated bone resorption outstrips bone formation, particularly in trabecular-rich sites like the vertebrae and hip.

3. Reduced Osteoblastic Function

- **Mechanism**:
  Osteoblasts, responsible for synthesizing bone matrix (osteoid) and promoting mineralization, decline in number and activity with age or disease.
- **Contributing Factors**:
  - **Aging**:
    Decreased osteoblast proliferation and differentiation, partly due to reduced growth factors (e.g., IGF-1, TGF-β).
  - **Hormonal Deficiency**:
    Oestrogen or testosterone loss impairs osteoblast function and survival.
  - **Wnt Signalling Disruption**:
    Impaired Wnt/β-catenin pathway, critical for osteoblast genesis, reduces bone formation.
- **Impact**:

Insufficient bone formation fails to compensate for resorption, leading to progressive bone loss.



This side depicts the process of old or damaged bone being broken down and removed. You can see large, multi-nucleated cells called **osteoclasts** (the irregular, ruffled cells actively "eating away" at the bone surface). These cells secrete acids and enzymes that dissolve the mineralized bone matrix, creating small depressions or pits. This is like the **"demolition crew"** of the bone, clearing out the old material.

This side shows the process of new bone being built. You can observe smaller, more cuboidal cells called **osteoblasts** arranged along a surface. These are the "construction workers" of the bone. They secrete a new organic bone matrix (called **osteoid**), which then gets mineralized (hardened) with calcium and phosphate. As the osteoblasts lay down new bone, some of them become trapped within the newly formed matrix and mature into **osteocytes** (the star-shaped cells embedded within the bone), which help maintain the bone tissue.

4. Calcium and Vitamin D Deficiency

- **Mechanism**:
  Inadequate calcium and/or vitamin D impair bone mineralization, triggering compensatory mechanisms that exacerbate bone loss.
- **Pathway**:
  - Low serum calcium or vitamin D reduces intestinal calcium absorption.
  - This stimulates parathyroid hormone (PTH) secretion, which increases osteoclastic resorption to mobilize calcium from bone.
  - Chronic PTH elevation further tilts remodelling toward resorption.
- **Impact**: Weakened bone matrix and reduced bone mineral density (BMD) increase fragility.

5. Age-Related Changes

- **Mechanisms**:
  - **Diminished Bone Turnover**:
    Aging reduces the efficiency of bone remodelling, with fewer active remodelling sites.
  - **Hormonal Decline**:
    Gradual loss of oestrogen (women) and testosterone (men) accelerates bone loss.
  - **Reduced Physical Activity**:
    Decreased mechanical loading on bones diminishes osteoblast stimulation (Wolff's Law).
  - **Oxidative Stress and Cellular Senescence**:
    Aging increases reactive oxygen species (ROS), impairing osteoblast function and promoting osteoclast activity.
- **Impact**: Cumulative bone loss, particularly in cortical and trabecular bone, heightens fracture risk in older adults.

6. Secondary Factors

- **Mechanisms**:
- Underlying conditions or external factors disrupt bone homeostasis, amplifying primary osteoporosis or causing secondary osteoporosis.
- **Key Contributors**:
  - **Medications**:
    - **Glucocorticoids**:
      Suppress osteoblast activity, promote osteoblast apoptosis, and enhance osteoclast survival, leading to rapid bone loss.
    - **Anticonvulsants**:
      Interfere with vitamin D metabolism, reducing calcium absorption.
    - **Proton Pump Inhibitors**:
      May impair calcium absorption over time.
  - **Endocrine Disorders**:
    - **Hyperthyroidism**:
      Increases bone turnover, favouring resorption.

- **Hyperparathyroidism**:
  Elevates PTH, driving osteoclastic activity.
- **Hypogonadism**:
  Reduces sex hormones, impairing bone formation.

  - **Other Conditions**:
    - **Gastrointestinal Diseases**:
      Malabsorption (e.g., celiac disease, IBD) reduces calcium and vitamin D uptake.
    - **Chronic Kidney Disease**:
      Impairs vitamin D activation and calcium homeostasis.
  - **Lifestyle Factors**:
    - **Smoking**:
      Impairs osteoblast function and reduces BMD.
    - **Excessive Alcohol**:
      Inhibits bone formation and increases fall risk.
    - **Sedentary Lifestyle**:
      Reduces mechanical stimulation of bone.

- **Impact**:
  These factors exacerbate bone loss, often requiring targeted treatment of the underlying cause alongside osteoporosis management.

Pathophysiological consequences

- **Structural Changes**:
  Loss of trabecular connectivity, cortical thinning, and increased bone porosity compromise bone strength.
- **Functional Outcomes**:
  Increased bone fragility leads to a higher risk of fragility fractures, particularly in the vertebrae, hip, and wrist.
- **Systemic Effects**:
  Pain, deformity (e.g., kyphosis), and functional limitations (e.g., reduced mobility) impact quality of life.

Clinical Relevance

Understanding the pathophysiology guides diagnostic and therapeutic strategies:

- **Diagnosis**:
  Bone mineral density (BMD) assessment via dual-energy X-ray absorptiometry (DXA), combined with fracture risk tools (e.g., FRAX®), identifies at-risk individuals.
- **Treatment**:
  Targets underlying mechanisms, including:
  - Antiresorptive therapies (e.g., bisphosphonates, denosumab) to reduce osteoclast activity.
  - Anabolic agents (e.g., teriparatide) to stimulate osteoblast function.
  - Calcium and vitamin D supplementation to support mineralization.
  - Lifestyle interventions (e.g., weight-bearing exercise, smoking cessation) to enhance bone health.

FRAGILITY FRACTURES

Fragility fractures are low-energy fractures resulting from minimal trauma, such as a fall from standing height or less, reflecting underlying bone fragility due to osteoporosis or other skeletal disorders.

A **fragility fracture** is a fracture that results from mechanical forces that would not ordinarily cause a fracture, known as **low-energy trauma**.

These fractures can occur across various skeletal sites but predominantly affect:

- **Vertebral Bodies**:
  These are the most common and often present as vertebral compression fractures. Many are asymptomatic or undiagnosed, detected incidentally on imaging. They may occur spontaneously or with minimal stress (e.g., lifting, coughing).
- **Proximal Femur (Hip Fractures)**:
  Highly debilitating, associated with significant morbidity, mortality, and loss of independence. Typically result from falls.
- **Proximal Humerus**:
  This condition is common in older adults and is often linked to falls on an outstretched arm, impacting shoulder function.
- **Distal Radius (Colles' Fracture)**:
  Frequently occurs from a fall on an outstretched hand, often an early indicator of osteoporosis.

Other sites, such as the pelvis, ribs, or long bones (e.g., femur, humerus), may also be affected, particularly in the context of falls. Vertebral fractures often develop insidiously, while appendicular fractures (e.g., hip, radius) are typically acute and trauma-related. Fragility fractures significantly increase the risk of subsequent fractures, emphasizing the need for early diagnosis and intervention.

Pathophysiology of Fragility Fractures

Fragility fractures result from **compromised bone strength**, primarily due to a **reduction in bone mass and deterioration of bone microarchitecture**. This structural weakening impairs the bone's ability to withstand even minimal mechanical stress or low-energy trauma (e.g., a fall from standing height).

Key underlying mechanisms include:

- **Osteoporosis** *(most common cause)*:
  Characterized by decreased bone mineral density (BMD) and structural deterioration of bone tissue, leading to increased fragility.
- **Osteopenia**:
  A precursor to osteoporosis, with mildly reduced BMD, predisposing bones to fracture under minimal force.
- **Bone Metastases**:
  Cancerous lesions disrupt normal bone remodelling, leading to localized weakening and higher fracture risk.
- **Chronic Corticosteroid Use**:

Inhibits osteoblast activity, enhances bone resorption, and reduces calcium absorption, accelerating bone loss.

- **Vitamin D Deficiency**:
  Impairs calcium absorption, leading to secondary hyperparathyroidism, increased bone turnover, and decreased bone strength.
- **Other Metabolic Bone Diseases**:
  - Paget's disease
  - Osteomalacia
  - Hyperparathyroidism

The cumulative effect of these conditions is a **reduction in both the quantity and quality of bone**, making it susceptible to fracture even with minimal trauma.

Fragility fractures may occur in almost all skeletal segments, but the preferential locations are the vertebral column, the proximal ends of the femur and humerus, and the distal end of the radius (Colles's fracture). Trauma due to a fall is by far the most frequent cause of fractures affecting long bones (femur, humerus, and radius), while it is more difficult to determine the cause and the exact time of fragility fractures of the vertebral body, which often go undiagnosed.

During patient evaluation, some clinical history details can suggest a vertebral fracture

Clinical Clues Suggestive of Vertebral Fractures

Vertebral compression fractures may be subtle or asymptomatic, but specific historical and physical findings can raise suspicion during clinical evaluation:

- **Historical Factors**:
  - History of recent low-energy trauma (e.g., minor fall, lifting).
  - Long-term corticosteroid use (≥3 months, e.g., prednisone), which accelerates bone loss.
  - Advanced age (risk increases significantly after age 65).
- **Physical and Functional Signs**:
  - **Spinal Deformities**:
    Progressive dorsal kyphosis ("dowager's hump") or lumbar lordosis due to vertebral collapse.
  - **Height Loss**:
    Loss of >6 cm (or >4 cm in a shorter timeframe) compared to peak adult height, often measured historically or via serial measurements.
  - **Reduced Rib-to-Iliac Crest Distance**:
    Distance <2 fingerbreadths (Wall-Occiput Test may also reveal increased occiput-to-wall distance).
  - **Dorso lumbar Pain**:
    Acute or chronic pain, often exacerbated by movement or palpation, though some fractures are painless.
  - **Postural Changes**:

Stooped posture or difficulty maintaining an upright stance.

- **Systemic Impacts**:
  - **Respiratory Dysfunction**: Kyphosis may reduce lung capacity, causing restrictive lung patterns or shortness of breath.
  - **Gastrointestinal Issues**: Altered thoracoabdominal mechanics may lead to early satiety, reflux, or constipation.

These findings, particularly when combined, warrant further evaluation with imaging (e.g., X-ray, CT, or MRI) to confirm vertebral fractures and assess their extent. Dual-energy X-ray absorptiometry (DXA) may also be indicated to evaluate bone mineral density (BMD) and guide osteoporosis management.

Fracture Risk Assessment and Clinical Implications

- **Fracture Risk Assessment:** Tools like FRAX® can estimate 10-year fracture probability, integrating clinical risk factors (e.g., age, prior fractures, corticosteroid use) with or without BMD data.
- **Management Implications:** Fragility fractures, especially vertebral, signal the need for comprehensive osteoporosis treatment, including pharmacologic therapy (e.g., bisphosphonates, denosumab), calcium /vitaminD supplementation, fall preven - tion strategies, and physical therapy to improve posture and strength.
- **Silent Fractures:** Up to two-thirds of vertebral fractures are asymptomatic, underscoring the importance of proactive screening in high-risk populations (e.g., postmenopausal women, older adults, or those on long-term glucocorticoids).

PRIMARY OSTEOPOROSIS

JUVENILE OSTEOPOROSIS

Juvenile osteoporosis refers to a rare form of osteoporosis occurring in children and adolescents, characterized by reduced bone mass, compromised bone strength, and increased fracture risk. It may arise from primary genetic or idiopathic causes or be secondary to other conditions or treatments. As a subset of primary osteoporosis, juvenile idiopathic osteoporosis (JIO) is diagnosed when no secondary cause is identified.

Aetiology

Juvenile osteoporosis encompasses a spectrum of conditions with diverse causes affecting bone development and integrity:

1. **Primary Causes**:
   - **Genetic Mutations**:

- **Quantitative/Qualitative Connective Tissue Defects**:
  Mutations affecting collagen or other bone matrix components, as seen in **osteogenesis imperfecta (OI)**, lead to fragile bones and often extra-skeletal manifestations (e.g., blue sclerae, hearing loss, dentinogenesis imperfecta).
- **Altered Osteoblastic Activity**:
  Impaired osteoblast function or differentiation predominantly affects trabecular bone, reducing bone formation and mineralization.

- **Idiopathic**:
  Juvenile idiopathic osteoporosis (JIO) is diagnosed when no genetic or secondary cause is identified, typically presenting with spontaneous fractures and low bone mineral density (BMD).

2. **Secondary Causes** (overlap with second - dary osteoporosis):
   - **Medical Conditions**:
     - **Leukaemia**:
       Bone marrow infiltration and chemo - therapy impair bone health.
     - **Chronic Inflammatory Diseases**:
       Conditions like juvenile idiopathic arthritis increase bone resorption via inflammatory cytokines.
     - **Prolonged Immobilization**:
       Reduced mechanical loading inhibits bone formation (Wolff's Law).
   - **Medications**:
     - **Glucocorticoids**:
       Long-term use suppresses osteoblast activity and promotes bone loss.
     - **Anti-epileptics**:
       Drugs like phenytoin impair vitamin D metabolism, reducing calcium absorption.
   - **Other**:
     Endocrine disorders (e.g., hypogon - adism) or nutritional deficiencies may contribute.

Pathophysiology

1. **Bone Remodelling Imbalance**:
   Increased osteoclastic resorption or reduced osteoblastic activity disrupts bone formation, particularly in trabecular bone, leading to low bone mass and structural weakness.
2. **Connective Tissue Defects**:
   In conditions like OI, abnormal collagen compromises bone matrix integrity, increasing fragility.
3. **Secondary Effects**:
   Chronic inflammation, immobilization, or medications exacerbate bone loss by altering bone turnover or mineralization.

Clinical Features

1. **Fragility Fractures**: Recurrent or spontaneous fractures, particularly vertebral

compression fractures or long bone fractures, are hallmark features.

2. **Skeletal Deformities**: May include kyphosis, scoliosis, or limb deformities, especially in OI.
3. **Growth Impairment**: Reduced bone mass may affect linear growth or skeletal maturation.
4. **Pain**: Bone pain or fracture-related discomfort, though vertebral fractures may be asymptomatic.
5. **Extra-skeletal Manifestations**: In OI, features like blue sclerae, joint hypermobility, or hearing loss may be present.

Diagnostic Criteria

The **International Society for Clinical Densitometry (ISCD) Paediatric Official Positions** (updated 2019) provide specific guidelines for diagnosing osteoporosis in children and adolescents, emphasizing fracture history and BMD:

- **Key Diagnostic Criteria**:
    - **Vertebral Fractures**:
      One or more vertebral fragility fractures (confirmed by imaging, e.g., X-ray or CT) establish the diagnosis, regardless of BMD.
    - **Long Bone Fractures**:
        - ≥2 fractures of long bones before age 10, OR
        - ≥3 fractures of long bones before age 19.
    - **Bone Mineral Density (BMD)**:
        - BMD Z-score ≤ -2.0 standard deviation (SD) at the **lumbar spine** or **total body less head (TBLH)**, measured via dual-energy X-ray absorptiometry (DXA).
        - Z-scores are age- and sex-matched, as T-scores (used in adults) are inappropriate for pediatric populations.
    - **Exclusion Criteria**:
      Fractures must not result from high-energy trauma, local pathologies (e.g., bone cysts), or other non-osteoporotic causes.
- **Diagnostic Notes**:
    - BMD alone is insufficient for diagnosis; fracture history is critical.
    - Vertebral fractures are often asymptomatic, requiring proactive imaging in at-risk children.
    - DXA interpretation must account for skeletal size, puberty stage, and ethnicity to avoid misdiagnosis.

Differential Diagnosis

- **Osteogenesis Imperfecta (OI)**: Distinguished by extra-skeletal features and genetic testing (e.g., COL1A1/COL1A2 mutations).

- **Secondary Osteoporosis**: Screen for underlying conditions (e.g., leukaemia, celiac disease, hyperthyroidism) or medication effects.
- **Rickets/Osteomalacia**: Caused by vitamin D deficiency or phosphate disorders, presenting with defective mineralization.
- **Non-accidental Trauma**: Must be ruled out in cases of recurrent fractures.

Management

Management of juvenile osteoporosis focuses on addressing underlying causes, optimizing bone health, and preventing fractures:

1. **Primary Interventions**:
   - **Calcium and VitaminD Supplemen - tation**:
     Ensures adequate mineralization, tailored to age-specific requirements.
   - **Physical Activity**:
     Weight-bearing exercises (e.g., walking, jumping) promote bone formation, adjusted for fracture risk.
   - **Pain Management**:
     For fracture-related discomfort, use analgesics or physical therapy.
2. **Pharmacologic Therapy** (case-specific):
   - **Bisphosphonates** (e.g., pamidronate):
     Used in severe cases (e.g., OI, JIO with recurrent fractures) to reduce osteoclastic activity and improve BMD. Administered intravenously in children to minimize gastrointestinal side effects.
   - **Monitoring**:
     Long-term use requires careful monitoring for side effects (e.g., osteonecrosis of the jaw, atypical fractures).
3. **Treatment of Secondary Causes**:
   - Manage underlying conditions (e.g., leukaemia, inflammatory diseases).
   - Minimize or adjust causative medications (e.g., glucocorticoids).
4. **Fracture Prevention**:
   - Fall prevention strategies (e.g., home safety modifications).
   - Orthopaedic interventions (e.g., bracing for vertebral fractures, surgical fixation for long bone fractures).
5. **Genetic Counselling**:
   For inherited conditions like OI, to guide family planning and management.

Prognosis

- **Juvenile Idiopathic Osteoporosis**:
  Often self-limiting, with improvement during puberty due to increased sex hormone production and bone accrual. However, severe cases may lead to persistent low BMD.
- **Osteogenesis Imperfecta**:
  Prognosis varies by subtype, with milder forms (e.g., Type I) allowing near-normal

life expectancy and severe forms (e.g., Type II) being lethal in infancy.

- **Secondary Osteoporosis**:
  Outcomes depend on control of the underlying condition and response to therapy.

Clinical Considerations

- **Screening**:
  High-risk children (e.g., those with chronic diseases, long-term glucocorticoid use, or recurrent fractures) should undergo BMD assessment and skeletal imaging.
- **Multidisciplinary Approach**:
  Involves paediatric endocrinologists, orthopaedists, geneticists, and physical therapists for comprehensive care.
- **Research Gaps**:
  Optimal duration and safety of bisphosphonate therapy in children remain under investigation.

POSTMENOPAUSAL OSTEOPOROSIS AND MALE OSTEOPOROSIS

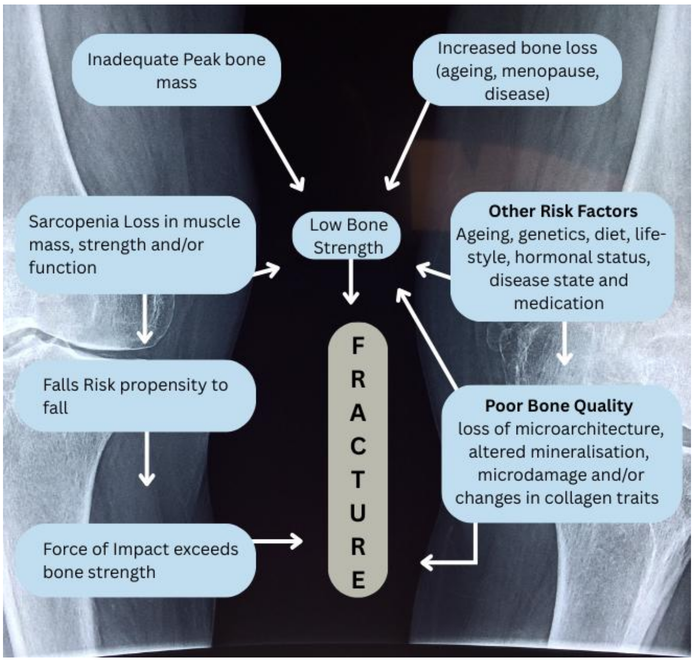
Postmenopausal Osteoporosis

1. Definition

- A primary form of osteoporosis triggered by **oestrogen deficiency** following meno - pause.
- Characterized by:
  - Rapid loss of **trabecular bone** (e.g., vertebrae, distal radius), leading to increased fracture risk.
  - High bone turnover with accelerated bone resorption.
  - Common fragility fractures (e.g., vertebral, hip, wrist).

2. Pathophysiology

- **Core Mechanism**:
  Oestrogen decline post-menopause removes its protective effect on bone, leading to **increased bone resorption** relative to formation.
- **Key Changes**:
  - **Increased Endosteal Resorption**: Osteoclasts erode bone on the inner (endosteal) surfaces, thinning trabecular and cortical bone.
  - **Decreased Periosteal Bone Formation**: Reduced osteoblast activity limits new bone formation on outer bone surfaces.
  - **Bone Marrow Expansion**: Replacement of bone with fatty marrow weakens structural integrity.
  - **Microarchitectural Perforation**: Loss of trabecular connectivity and thinning of trabeculae increase bone fragility.
- **Bone Type Affected**: Trabecular bone (spongy, found in vertebrae and distal radius) is more affected than cortical bone due to its higher turnover rate.



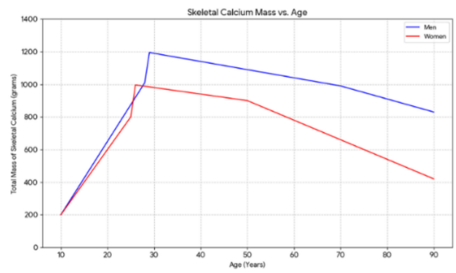
3. Diagnosis

- **Gold Standard**:
  Dual-energy X-ray Absorptiometry (DXA) to measure **Bone Mineral Density (BMD)**.
- **Diagnostic Criteria** (WHO):
  - **T-score ≤ -2.5 SD** at the lumbar spine, femoral neck, or total hip compared to a young adult female reference population confirms osteoporosis.
  - **T-score between -1.0 and -2.5 SD** indicates osteopenia (low bone mass).
- **Additional Tools**:
  Fracture risk assessment (e.g., **FRAX®**) integrates BMD with clinical risk factors to estimate 10-year fracture probability.

Indications for DXA in Postmenopausal Women

Screening is recommended based on risk factors to identify those at high risk of fractures:

- **At Any Age with ≥1 Major Risk Factor**:
  - History of **fragility fracture** (low-energy trauma, e.g., fall from standing height).
  - **Maternal hip fracture** before age 75.
  - **Early menopause** (<45 years, including surgical menopause).
  - **Low BMI** (<19 kg/m², indicating reduced mechanical loading).
  - **Long-term glucocorticoid use** (≥3 months, e.g., prednisone ≥5 mg/day).
- **Postmenopausal Women with ≥3 Minor Risk Factors**:
  - **Age >65 years** (risk increases with advancing age).
  - **Family history** of severe osteoporosis (e.g., parental fractures).
  - **Premenopausal amenorrhea** (>6 months, excluding pregnancy, indicating oestrogen deficiency).
  - **Low calcium intake** (<1200 mg/day, impairing mineralization).
  - **Heavy smoking** (>20 cigarettes/day) impairs osteoblast function.
  - **Excessive alcohol** (>60 g/day, ~4-5 standard drinks) disrupts bone remodelling.



The graph shows:
- Bone mass generally increases during childhood and adolescence, peaking in early adulthood (around late 20s for men and early to mid-20s for women).
- Men typically achieve a higher peak bone mass than women.
- After peak bone mass, there's a gradual decline for both genders.
- Women experience a more rapid decline in bone mass around menopause (typically in their late 40s to early 50s) due to hormonal changes.
- The decline continues with increasing age for both, but women generally have a lower bone mass in older age compared to men.

Male Osteoporosis

1. Definition

- A form of osteoporosis in men, less common than in women, characterized by reduced bone mass and increased fracture risk.
- Accounts for:
  - ~20% of all hip fractures.
  - ~50% of vertebral fracture incidence compared to women.
- Aetiology:
  Predominantly **secondary** (2/3 of cases) due to underlying conditions or medications; primary cases are often age-related or idiopathic.

2. Pathophysiology

- **Core Mechanism**:
  Declining testosterone and/or oestrogen levels (men convert testosterone to oestrogen via aromatase) increase bone resorption and reduce formation.
- **Key Changes**:
  - Loss of trabecular and cortical bone, though cortical bone loss is more prominent in men.
  - Secondary causes (e.g., hypogonadism, glucocorticoids) amplify bone turnover imbalance.
  - Age-related decline in muscle mass (sarcopenia) increases fall risk, contributing to fractures.
- **Common Secondary Causes**:
  - Hypogonadism (low testosterone).
  - Glucocorticoid use.
  - Alcoholism, smoking, or chronic diseases (e.g., COPD, hyperthyroidism, malabsorption).

3. Diagnosis

- **Gold Standard**: **DXA** to measure BMD.
- **Diagnostic Criteria**:
  - **T-score ≤ -2.5 SD** at the lumbar spine, femoral neck, or total hip compared to a young adult male reference population.
  - Same WHO criteria as for women, though male-specific reference databases are used.
- **Clinical Note**:
  Always evaluate for **secondary causes** (e.g., hypogonadism, vitamin D deficiency, malignancy) due to their high prevalence in men.

Indications for DXA in Men

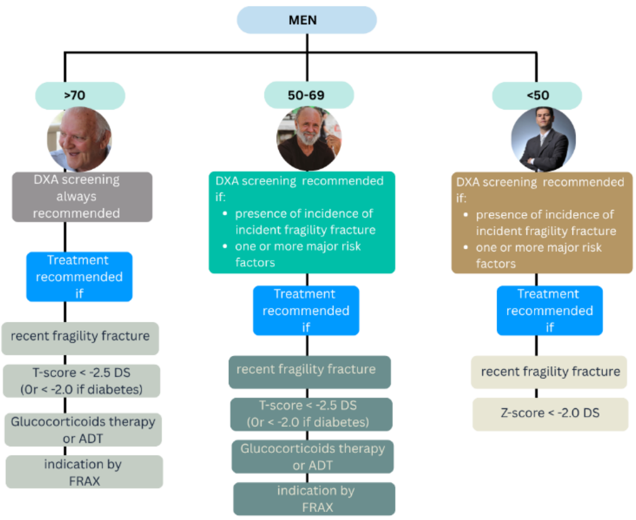
Screening is targeted based on risk factors:

- **At Any Age with ≥1 Major Risk Factor**:

- History of **fragility fracture.**
- **Long-term glucocorticoid use** (≥3 months).
- **Hypogonadism** (clinical or biochemical evidence).

- **Men >60 Years with ≥3 Minor Risk Factors**:
  - **Family history** of osteoporosis or fractures.
  - **Low BMI** (<19 kg/m²).
  - **Low calcium intake** (<1200 mg/day).
  - **Heavy smoking** (>20 cigarettes/day).
  - **Excessive alcohol** (>60 g/day).

PROPOSED INDICATIONS FOR DXA SCREENING AND TREATMENT IN MEN



4. Clinical Considerations

- **Postmenopausal Osteoporosis**:
  - **Fracture Risk**:
    Vertebral fractures are most common, often asymptomatic; hip fractures carry high morbidity.
  - **Management**:
    Antiresorptive therapies (e.g., bisphosph-onates, denosumab), calcium/vitamin D supplementation, and lifestyle modifications (e.g., weight-bearing exercise, smoking cessation).
  - **Prevention**:
    Early screening and hormone replacement therapy (HRT) in select cases (e.g., early menopause) can mitigate bone loss.
- **Male Osteoporosis**:
  - **Diagnostic Workup**:
    Include testosterone levels, 25-hydroxyvitamin D, and screening for secondary causes (e.g., hyperthyroidism, multiple myeloma).
  - **Management**:
    Similar to women, with bisphosphonates as first-line; testosterone replacement may be considered in hypogonadism.
  - **Challenges**:
    Underdiagnosis due to lower awareness and fewer screening guidelines for men.
- **Shared Strategies**:
  - **Fall Prevention**:
    Address environmental hazards and improve muscle strength/balance.
  - **Fracture Risk Tools**:
    FRAX® or similar tools guide treatment decisions.
  - **Monitoring**: Repeat

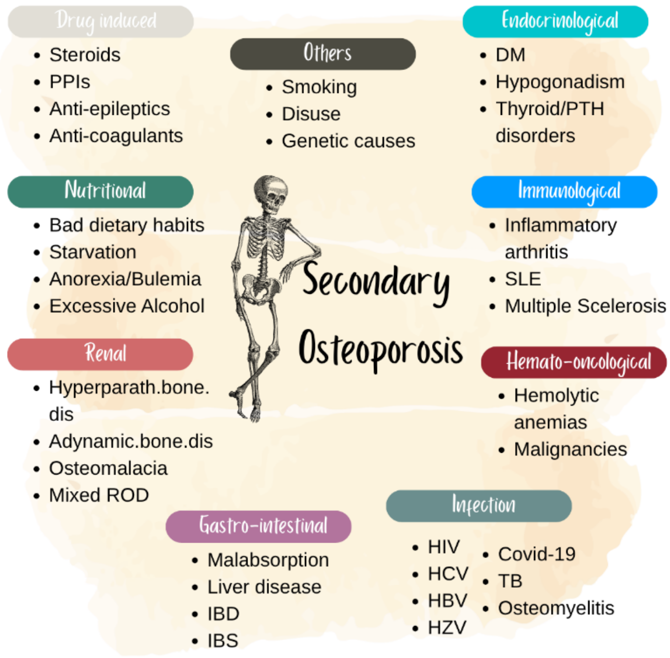
DXA every 1-2 years to assess treatment response or progression.

SECONDARY OSTEOPOROSIS

A form of osteoporosis caused by underlying medical conditions, medications, or lifestyle factors that accelerate bone loss or impair bone formation, leading to reduced bone mass, compromised bone strength, and increased fracture risk. Unlike primary osteoporosis, which is primarily age- or hormone-related, secondary osteoporosis results from identifiable causes such as endocrine disorders (e.g., hyperthyroidism, hyperparathyroidism), gastrointestinal diseases (e.g., celiac disease, inflammatory bowel disease), prolonged use of medications (e.g., glucocorticoids, anticonvulsants), or lifestyle factors (e.g., excessive alcohol, smoking). It often requires treatment of the underlying cause alongside bone-specific therapies.

COMMON CAUSES OF SECONDARY OSTEOPOROSIS

CATEGORY	EXAMPLES
Endocrine Disorders	Cushing's syndrome, hyper thyroidism, hyperparathyroidism, hypogonadism, diabetes mellitus
Gastrointestinal Disorders	Celiac disease, inflammatory bowel disease (IBD), chronic liver disease, and gastric bypass
Hematologic Disorders	Multiple myeloma, leukaemia, lymphoma, thalassemia
Rheumatologic Conditions	Rheumatoid arthritis, systemic lupus erythematosus (SLE)
Chronic Medication Use	Glucocorticoids, anticonvulsants, heparin, proton pump inhibitors
Nutritional Deficiencies	Low calcium or vitamin D, anorexia nervosa, and alcoholism
Renal Disorders	Chronic kidney disease, renal tubular acidosis
Miscellaneous	HIV/AIDS, organ transplantation, and immobilization



GLUCOCORTICOID-INDUCED OSTEOPOROSIS (GIOP)

Definition

Glucocorticoid-induced osteoporosis (GIOP) is a form of **secondary osteoporosis** characterized by **bone loss** and **increased fracture risk** due to chronic exposure to glucocorticoids.

- **Exogenous**:
  Medications (e.g., prednisone, dexamethasone) used for autoimmune, inflammatory, or other conditions (e.g., rheumatoid arthritis, asthma, organ transplantation).
- **Endogenous**:
  Excess cortisol production, as in **Cushing's syndrome**. GIOP is the most common cause of secondary osteoporosis,

significantly impacting bone strength and leading to fragility fractures.

Mechanisms

Glucocorticoids disrupt bone homeostasis through multiple pathways, favouring bone resorption over formation and impairing bone quality:

1. **Inhibition of Osteoblast Activity**:
   - Suppresses osteoblast proliferation, diff -erentiation, and survival.
   - Reduces synthesis of bone matrix (collagen and osteoid) via downregulation of growth factors (e.g., IGF-1, TGF-β).
   - Promotes osteoblast and osteocyte apoptosis, limiting bone formation.
2. **Stimulation of Osteoclast Activity**:
   - Increases RANKL expression and decreases osteoprotegerin (OPG), enhancing osteoclastogenesis and bone resorption.
   - Prolongs osteoclast lifespan, accelerating bone breakdown.
3. **Impaired Calcium Homeostasis**:
   - **Decreased Intestinal Calcium Absorption**:
     Inhibits vitamin D-dependent calcium uptake in the gut.
   - **Increased Urinary Calcium Excretion**:
     Promotes renal calcium loss, leading to secondary hyperparathyroidism, which further stimulates osteoclast activity.
4. **Reduced Gonadal Hormones**:
   - Suppresses the hypothalamic-pituitary-gonadal axis, lowering oestrogen and testosterone levels, which are critical for maintaining bone mass.
   - Contributes to bone loss in both men and women.
5. **Indirect Effects via Muscle**:
   - Induces **steroid myopathy**, reducing muscle mass and strength.
   - Decreases physical activity and mechanical loading on bones (Wolff's Law), further impairing bone formation.
6. **Bone Quality Deterioration**:
   - Alters bone microarchitecture (e.g., trabecular thinning, loss of connectivity).
   - Impairs bone material properties, increasing fragility beyond what BMD indicates.

Timeline & Risk

- **Onset**:
  Bone loss begins **early**, within the **first 3–6 months** of glucocorticoid therapy, with peak loss in the **first 6–12 months**.
- **Bone Type Affected**:
  Trabecular bone (e.g., vertebrae, ribs) is most vulnerable due to its high turnover

rate, though cortical bone is also affected over time.

- **Fracture Risk**:
  - Fragility fractures occur in **30–50% of patients** within 5 years of chronic glucocorticoid use.
  - **Vertebral fractures** are most common, often asymptomatic, followed by hip and non-vertebral fractures.
  - Fracture risk is **higher than predicted by BMD** due to impaired bone quality and microarchitecture.
- **High-Risk Groups**:
  - **Higher doses** (e.g., prednisone ≥7.5 mg/day or equivalent).
  - **Older age** (>60 years).
  - **Postmenopausal women** (compounded by oestrogen deficiency).
  - **Prior fragility fractures**.
  - **Underlying inflammatory diseases** (e.g., rheumatoid arthritis, which independently increase bone loss).
- **Risk Decline**:
  Fracture risk decreases rapidly after discontinuation of glucocorticoids, though some bone loss may persist.

Dose & Duration Impact

Glucocorticoid dose, duration, and administration route significantly influence GIOP risk:

FACTOR	EFFECT
Systemic Glucocorticoids	High risk, dose- and duration-dependent. Prednisone ≥5 mg/day for ≥3 months significantly increases risk.
Inhaled Glucocorticoids	Controversial. High doses (>800 mcg/day budesonide or equivalent) may pose a risk, particularly in susceptible patients.
No Safe Threshold	Even low doses (e.g., <5 mg/day prednisone) may increase fracture risk in vulnerable individuals (e.g., elderly, low BMD).

- **Cumulative Dose**:
  Lifetime exposure amplifies risk, even with intermittent use.
- **Alternate-Day Regimens**:
  May reduce risk, but do not eliminate it.

Key Diagnostic Points

- **BMD Assessment**:
  - **Dual-energy X-ray Absorptiometry (DXA)** is the gold standard to measure **Bone Mineral Density (BMD)**.
  - **T-score ≤ -2.5 SD** at the lumbar spine, femoral neck, or total hip confirms osteoporosis (per WHO criteria).
  - **Limitations**: BMD underestimates fracture risk in GIOP, as bone quality (microarchitecture, material properties) is disproportionately affected.
- **Fracture Risk Assessment**:
  - Tools like **FRAX®** (adjusted for glucocorticoid use) estimate 10-year fracture probability, integrating BMD

and clinical risk factors (e.g., dose, duration, age).
  - Vertebral imaging (X-ray, VFA via DXA) is critical to detect asymptomatic vertebral fractures.
- **Screening Recommendations**:
  - **Early DXA** for patients on **glucocorticoids ≥3 months** (prednisone equivalent ≥5 mg/day).
  - Consider baseline DXA before initiating long-term therapy in high-risk groups (e.g., postmenopausal women, older men, prior fractures).
  - Repeat DXA every **1–2 years** to monitor BMD changes.
- **Prophylaxis Consideration**:
  - Initiate **bone-protective therapy** con - currently with glucocorticoids in high-risk patients, regardless of baseline BMD (e.g., postmenopausal women, T-score < -1.5 SD, or FRAX high-risk).

Clinical Considerations

- **High-Risk Identification**:
  - Screen for **secondary causes** (e.g., vitamin D deficiency, hypogonadism) that may compound GIOP.
  - Assess fall risk due to steroid-induced myopathy or comorbidities.
- **Management**:
  - **Minimize Glucocorticoid Use**: Use the lowest effective dose and shortest duration; consider steroid-sparing agents.
  - **Pharmacologic Therapy**:
    - **Bisphosphonates** (e.g., alendronate, risedronate): First-line to reduce osteoclast activity and fracture risk.
    - **Denosumab**: Alternative for high-risk patients or bisphosphonate intolerance.
    - **Teriparatide**: Anabolic agent for severe cases or multiple fractures.
  - **Calcium and Vitamin D**: Ensure **1200–1500 mg/day calcium** and **800–2000 IU/day vitamin D** to support mineralization.
  - **Lifestyle**: Weight-bearing exercise, smoking cessation, and alcohol moderation to enhance bone health.
- **Monitoring**:
  - Regular BMD and fracture risk reassessment.
  - Monitor for treatment side effects (e.g., osteonecrosis of the jaw with bisphosphonates).
- **Prevention**:
  - Prophylactic therapy for patients on **≥3 months of glucocorticoids** with high

fracture risk (per guidelines, e.g., ACR 2017).
  - Fall prevention strategies (e.g., physical therapy, home safety modifications).

ORGAN TRANSPLANT OSTEOPOROSIS

Definition

Organ transplant osteoporosis is a form of **secondary osteoporosis** characterized by **reduced bone mass, compromised bone strength**, and **increased fracture risk** in patients undergoing **solid organ transplantation** (e.g., kidney, heart, liver, lung). It results from a combination of pre-transplant bone fragility due to underlying organ disease and post-transplant factors, primarily **immunosuppressive therapy** (e.g., glucocorticoids) and persistent metabolic abnormalities.

Prevalence and Timeline

- **Pre-Transplant**:
  - **Fragility Fractures**:
    Approximately **10–15%** of patients awaiting solid organ transplants (kidney, heart, liver, lung) experience fragility fractures due to the negative effects of chronic organ failure on bone health.
  - **Contributing Factors**:
    Underlying conditions (e.g., renal osteodystrophy, liver disease, heart failure) impair bone quality and mineralization.
- **Post-Transplant**:
  - **Bone Loss**:
    Rapid and significant bone loss occurs, with the **greatest decline in the first-year** post-transplant (up to 10–20% BMD loss in some cases).
  - **Persistent Loss**:
    Bone loss continues at a **slower rate** in subsequent years, influenced by ongoing immunosuppressive therapy and metabolic factors.
  - **Fracture Incidence**:
    - **Vertebral Fractures**:
      Peak within the **first 3 years** post-transplant, affecting **30–40%** of patients.
    - **Other Sites**:
      Hip and non-vertebral fractures also occur, though less frequently.

Mechanisms and Risk Factors

Organ transplant osteoporosis results from a complex interplay of pre- and post-transplant factors that disrupt bone remodelling and quality:

- **Pre-Transplant Factors**:
  - **Underlying Organ Disease**:
    - **Kidney Failure**:
      Leads to **renal osteodystrophy**, including secondary hyperpara -

thyroidism, vitamin D deficiency, and impaired bone mineralization.

- **Liver Disease**:
  Causes vitamin D malabsorption, hypogonadism, and reduced osteoblast activity (e.g., in cholestatic liver disease).
- **Heart/Lung Failure**:
  Associated with immobility, inflammation, and malnutrition, all of which impair bone health.

- **Metabolic Abnormalities**:
  Chronic illness often results in low calcium, vitamin D deficiency, and hypogonadism, contributing to bone fragility.

- **Post-Transplant Factors**:
  - **Immunosuppressive Therapy**:
    - **Glucocorticoids**:
      Primary driver of bone loss, especially at **high doses** in the early post-transplant period (e.g., prednisone 20–60 mg/day initially).
      - Inhibits osteoblast activity, promotes osteoblast apoptosis, and stimulates osteoclast activity.
      - Reduces intestinal calcium absorption and increases urinary calcium excretion, leading to secondary hyperparathyroidism.
      - Induces steroid myopathy, reducing physical activity and mechanical bone loading.
    - **Calcineurin Inhibitors** (e.g., cyclo - sporine, tacrolimus):
      May contribute to bone loss by increasing bone turnover or causing renal magnesium wasting.
  - **Persistent Secondary Hyperparathyroidism**:
    - Affects up to **50% of kidney transplant recipients**, even with functioning grafts.
    - Elevated parathyroid hormone (PTH) levels drive osteoclastic resorption, particularly in cortical bone, leading to bone loss and fragility.
  - **Other Immunosuppressants**:
    Mammalian target of rapamycin (mTOR) inhibitors (e.g., sirolimus) may have variable effects, with some evidence suggesting less bone toxicity.

- **General Risk Factors**:
  - **Older Age**:
    Increases baseline fracture risk and exacerbates bone loss.
  - **Female Gender**:
    Postmenopausal women are at higher risk due to estrogen deficiency.
  - **Low BMD Pre-Transplant**:
    Pre-existing osteopenia or osteoporosis amplifies post-transplant fracture risk.

- **Immobility**:
  Post-surgical recovery or chronic illness reduces weight-bearing activity, impairing bone formation.
- **Nutritional Deficiencies**:
  Persistent low calcium, vitamin D, or protein intake hinders bone mineralization.

Diagnosis

- **Bone Mineral Density (BMD)**:
  - **Dual-energy X-ray Absorptiometry (DXA)**:
    Gold standard to assess BMD at the lumbar spine, femoral neck, or total hip.
  - **T-score ≤ -2.5 SD**:
    Confirms osteoporosis (per WHO criteria), though fracture risk in transplant patients is often higher than BMD suggests due to impaired bone quality.
  - **Screening**:
    Recommended **pre-transplant** and **within 6–12 months post-transplant** for high-risk patients (e.g., glucocorticoid use, prior fractures).
- **Fracture Assessment**:
  - **Vertebral Imaging**:
    X-ray or vertebral fracture assessment (VFA) via DXA to detect asymptomatic vertebral fractures, which are common (30–40% incidence).
  - **Fracture Risk Tools**:
    FRAX® (adjusted for glucocorticoid use) estimates 10-year fracture probability, though it may underestimate risk in transplant patients.
- **Laboratory Evaluation**:
  - Assess **calcium**, **vitamin D (25-hydroxyvitamin D)**, **PTH**, **phosphorus**, and **renal function** to identify metabolic contributors (e.g., secondary hyperparathyroidism).
  - Screen for **hypogonadism** (testosterone in men, oestradiol in premenopausal women) and other endocrine disorders.

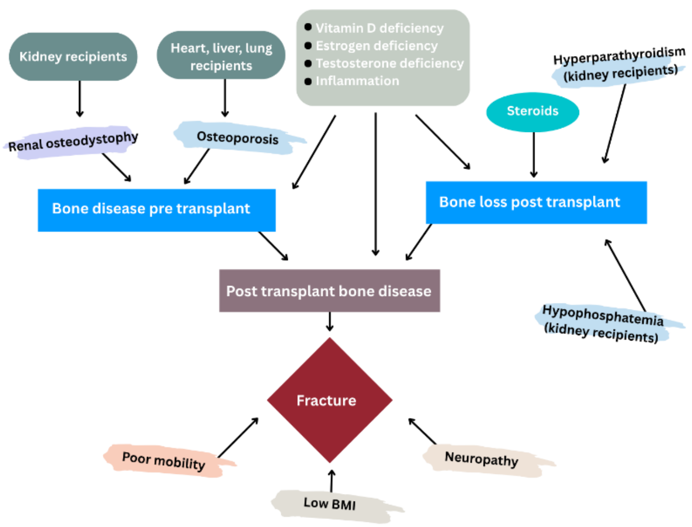
Clinical Considerations

- **High-Risk Periods**:
  - **First Year Post-Transplant**:
    Rapid bone loss due to high-dose glucocorticoids and surgical stress.
  - **First 3 Years**:
    Peak vertebral fracture incidence, necessitating proactive monitoring and intervention.
- **Management**:
  - **Minimize Glucocorticoids**:
    Use the lowest effective dose; consider rapid tapering or steroid-sparing regimens (e.g., mycophenolate, calcineurin inhibitors) when feasible.
  - **Pharmacologic Therapy**:

- **Bisphosphonates** (e.g., alendronate, zoledronic acid):
  First-line to reduce bone resorption; often initiated pre- or early post-transplant in high-risk patients.
- **Denosumab**:
  Alternative for patients with renal impairment or bisphosphonate intolerance.
- **Teriparatide**:
  Considered for severe osteoporosis or multiple fractures to stimulate bone formation.

- **Calcium and Vitamin D**:
  - Ensure **1200–1500 mg/day calcium** (dietary or supplements).
  - Maintain **25-hydroxyvitamin D >30 ng/mL** with 800–2000 IU/day vitamin D or higher doses if deficient.
- **Management of Hyperparathyroidism**:
  - **Calcimimetics** (e.g., cinacalcet) or **parathyroidectomy** for persistent secondary hyperparathyroidism in kidney transplant recipients.
  - Monitor PTH and calcium levels closely.
- **Lifestyle**:
  - Encourage **weight-bearing and resistance exercise** to improve bone and muscle strength, tailored to post-transplant recovery.
  - Promote **smoking cessation** and **alcohol moderation** to reduce bone loss.
- **Fall Prevention**: Address myopathy, optimize mobility, and modify home environments to reduce fall risk.

- **Monitoring**:
  - **BMD**:
    Repeat DXA every **1–2 years** or as clinically indicated.
  - **Fracture Surveillance**:
    Routine vertebral imaging in high-risk patients (e.g., glucocorticoid use >3 months).
  - **Metabolic Markers**:
    Regular assessment of bone turnover markers (e.g., CTX, P1NP) may guide therapy in complex cases.



DRUG-INDUCED OSTEOPOROSIS

Definition

Drug-induced osteoporosis is a form of **secondary osteoporosis** characterized by **reduced bone mass, compromised bone strength**, and **increased fracture risk** resulting from medications that disrupt bone homeostasis. These drugs impair **bone formation**, accelerate **bone resorption**, or interfere with **calcium and vitamin D metabolism**, leading to bone fragility and predisposition to fragility fractures.

Key Drug Classes & Associated Fracture Risks

DRUG CLASS	EXAMPLES	MECHANISM	FRACTURE RISK NOTES
Glucocorticoids	Prednisone, Dexamethasone	↓ Osteoblast activity, ↑ Osteoclast activity	High risk, especially within the first 6–12 months
Aromatase Inhibitors	Letrozole, Anastrozole	Oestrogen suppression → ↑ Bone resorption	Strong association with fragility fractures
Proton Pump Inhibitors (PPIs)	Omeprazole, Esomeprazole	↓ Calcium absorption	Risk ↑ with >12 months of use, especially hip/vertebral fractures
SSRIs (Selective Serotonin Reuptake Inhibitors)	Fluoxetine, Sertraline	Interfere with bone metabolism	↑ Risk of hip fractures, especially >70 years; the effect appears within the first year
Thyroid Hormones (in suppressive doses)	Levothyroxine	Iatrogenic hyperthyroidism → ↑ Bone turnover	↑ Risk of osteoporotic fractures
Thiazolidinediones (Glitazones)	Pioglitazone, Rosiglitazone	Promote adipogenesis over osteoblastogenesis	↑ Risk of hip/humerus fractures, especially in postmenopausal women (3–4× higher)
Anticonvulsants	Phenytoin, Carbamazepine, Phenobarbital	↑ Vitamin D catabolism, ↓ BMD	↑ Risk of hip fractures (2–6×), especially with polytherapy
Heparins	Unfractionated heparin	Impairs bone formation	↑ Fracture risk with long-term use
Warfarin	–	Inhibits vitamin K-K-dependent bone proteins	Data is inconclusive/controversial

Clinical Considerations

- **Duration-Dependent**:
  Fracture risk often correlates with **prolonged therapy**.
- **Age-Sensitive**:
  Older adults, especially postmenopausal women and individuals >70 years, are **more vulnerable**.
- **Combination Risk**:
  Some drugs (e.g., SSRIs + bisphosphonates) may negate therapeutic benefits or increase risk.

Monitoring & Management

- **DXA Scan**:
  Recommended for patients on long-term therapy with high-risk drugs.
- **Supplementation**:
  Ensure adequate **calcium and vitamin D** intake.
- **Fall Prevention**:
  Particularly critical in elderly patients.
- **Alternative Medications**:
  Use the lowest effective dose or consider substitutes with lower skeletal risk, if possible.
- **Pharmacologic Interventions**:
  Consider bisphosphonates or denosumab for high-risk patients.

THE EPIDEMIOLOGICAL IMPACT OF OSTEOPOROSIS

Osteoporosis represents a growing public health burden with profound implications for morbidity, mortality, and healthcare resource utilization worldwide. In the United States alone, an estimated **3.5 million women** and **1 million men** are currently affected by osteoporosis. With the aging population projected to rise substantially, specifically, a **25% increase in the over-65 age group over the next 25 years**, a proportional surge in osteoporosis-related complications is anticipated.

Fracture Epidemiology and Underdiagnosis

Among individuals aged **50 years and older**, annual hip fractures exceeded **90,000 cases**, while emergency departments reported more than **70,000 vertebral fractures** in 2010. However, since vertebral fractures are frequently asymptomatic or underdiagnosed, the true incidence may be **ten times higher** than reported. This highlights a significant gap in detection and management, contributing to the "silent epidemic" nature of the disease.

Mortality and Morbidity

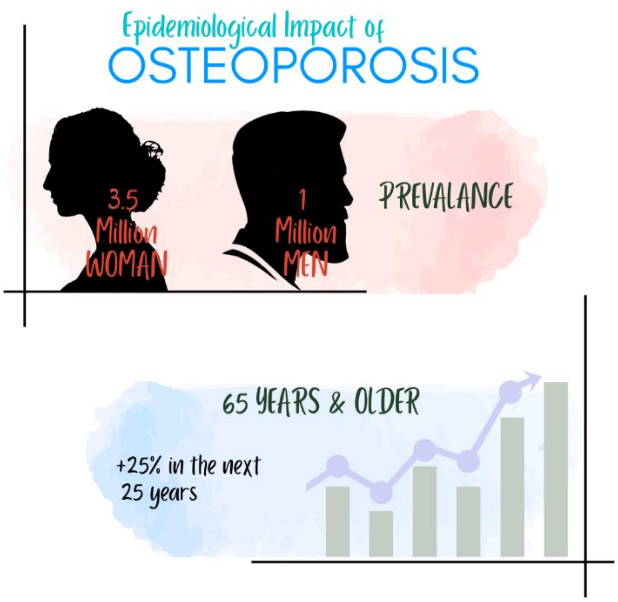
Fractures due to osteoporosis, particularly those involving the **hip and vertebrae**, are associated with **significantly increased mortality**:

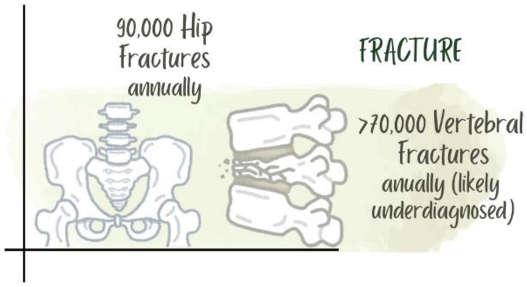
- **Hip fractures** increase the **relative risk of death 5–8 fold** in the **first three months** post-fracture.
- **Mortality rates** remain elevated **up to 10 years**, with absolute mortality reaching:
  - **9% at 1 month**
  - **36% at 1 year**
- This rate is **comparable to that of stroke and breast cancer**, and **quadruple** that of endometrial cancer.

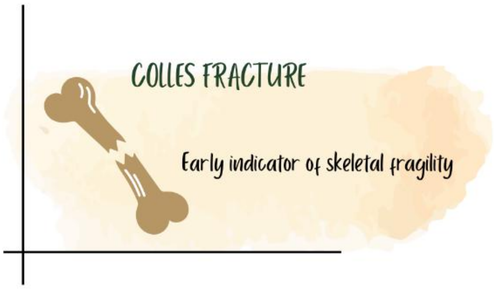
Beyond mortality, **50% of women** who experience a hip fracture report a **substantial decline in functional independence**, with **~20% requiring long-term institutional care**.

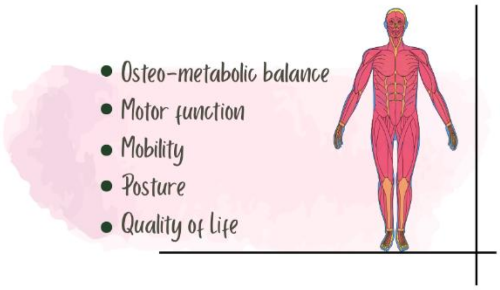
Colles' Fracture as a Sentinel Event

Colles' fractures (distal radius fractures) often represent the **first clinical sign of skeletal fragility**, serving as a sentinel event that predicts a higher risk of subsequent fractures, particularly **hip fractures**. Early identification and intervention at this stage are crucial for secondary-prevention









Functional and Quality of Life Impact

Osteoporotic fractures result in:

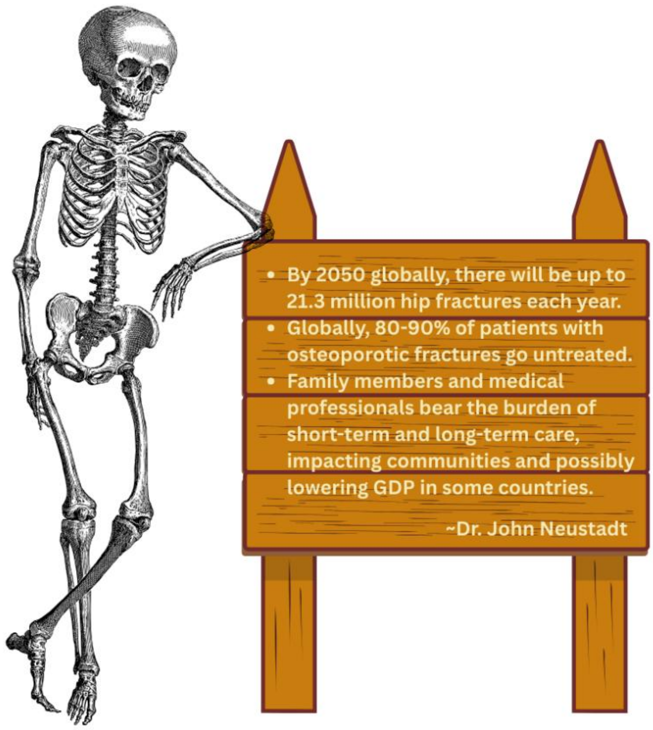
- Chronic **pain and disability**
- **Reduced mobility**, **postural instability**, and **impaired gait**
- **Loss of independence**, psychological distress, and **social isolation**
- Marked **decline in quality of life** and daily functioning

ICF-Based Functional Classification

Utilizing the **International Classification of Functioning, Disability and Health (ICF)** framework, a comprehensive understanding of the functional deficits in osteoporosis has been established. These include disturbances in:

- **Osteo-metabolic balance**
- **Motor function and coordination**
- **Posture, balance, and mobility**
- **Gait dynamics**
- **Psychosocial and environmental inter - action**
- **Overall quality of life**

The development of a tailored **"ICF Core Set for Osteoporosis"** enables a structured, multidimensional approach to rehabilitation and care planning, ensuring that interventions target the most relevant areas of disability in this population.



CAUSES OF OSTEOPOROSIS

Osteoporosis is a skeletal disorder characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fractures. According to the World Health Organization (WHO), osteoporosis is defined by a BMD T-score of −2.5 or lower, measured via dual-energy X-ray absorptiometry (DXA), the current diagnostic gold standard.

It is estimated that **1 in 2 women and 1 in 5 men over 50 years** will suffer from an osteoporotic fracture, with **approximately 44 million Americans** at risk. The most common fracture sites include the hip, spine (vertebrae), and wrist. Despite effective therapies to reduce bone resorption, osteoporosis often remains undiagnosed until after a fracture, underscoring the need for **early identification and preventive strategies**.

Pathophysiology: Uncoupling of Bone Remodelling

Bone remodelling is a dynamic process involving a balance between bone-forming osteoblasts and bone-resorbing osteoclasts. In osteoporosis, this equilibrium becomes disrupted **bone resorption exceeds formation**, leading to progressive bone loss.

- **Peak bone mass** is typically achieved in early adulthood.
- **Aging**, **hormonal changes**, and **inflammatory states** accelerate the natural rate of bone loss.

Hormonal Contributions

1. **In Women**

- **Estrogen deficiency**—especially after menopause—is a **primary driver** of accelerated bone resorption.
- Estrogen supports osteoblast survival and inhibits osteoclastogenesis by:
  - Reducing osteoclast formation
  - Enhancing osteoclast apoptosis
  - Promoting osteoblast-mediated bone formation

2. **In Men**

- **Testosterone** and its **conversion to estrogen** via aromatization are both critical to male bone health.
- Loss of androgen receptor function in bone cells is linked to male osteoporosis.
- **Dual hormonal protection** in men includes:
  - Direct anabolic action of testosterone
  - Estrogen-mediated suppression of bone resorption

Secondary Causes of Osteoporosis

Secondary osteoporosis refers to bone loss resulting from **underlying pathological or external causes**. These include:

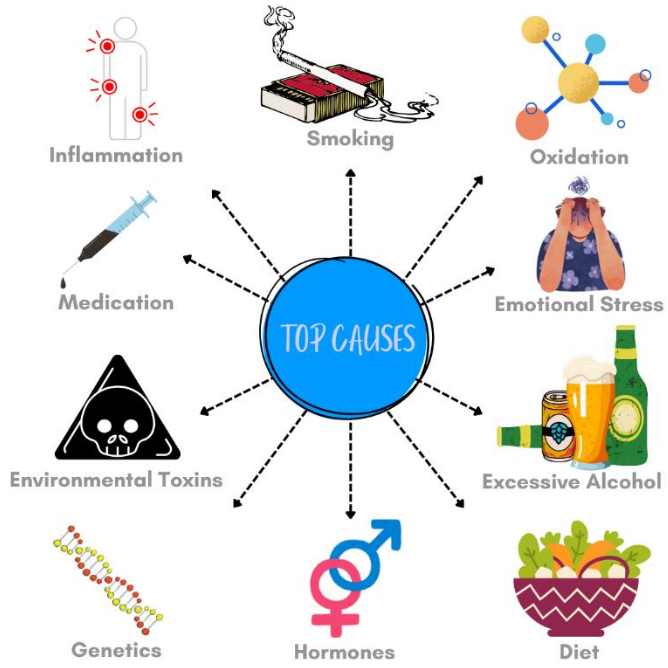
- **Chronic glucocorticoid therapy** (iatro - genic)
- **Hypogonadism** (both male and female)
- **Malnutrition** and **eating disorders** (e.g., anorexia nervosa)
- **Excessive physical activity** with low energy availability
- **Neoplastic disorders**
- **Endocrinopathies** (e.g., hyperthyroidism, hyperparathyroidism)
- **Chronic inflammatory conditions**

Metabolic and Neuroendocrine Interactions

- **Energy balance and bone mass** are tightly interconnected.
- Hormonal signals such as **leptin**, involved in appetite regulation, also modulate bone remodelling.
- Anti-obesity treatments and **long-term use of selective serotonin reuptake inhibitors (SSRIs)** have been implicated in reduced bone density.

Diagnostic and Economic Implications

While DXA remains the diagnostic benchmark, **routine population screening is not currently cost-effective**, necessitating alternative methods to identify at-risk individuals earlier. Given the **significant healthcare burden** associated with osteoporotic fractures, especially hip fractures, **early diagnosis, preventive strategies, and treatment** are vital to reducing morbidity, mortality, and healthcare costs.



RISK FACTORS OF OSTEOPOROSIS

Fracture risk in osteoporosis results from a complex interplay between bone-intrinsic factors and extra-skeletal contributors. While **bone mineral density (BMD)** remains a critical determinant, **other independent and modifiable risk factors** also contribute significantly to fracture susceptibility.

Risk factors are typically categorized into:

1. **BMD-dependent** (e.g., low bone mass),
2. **BMD-independent** (e.g., prior fractures, age-related changes), and
3. **Extra-osseous** (e.g., fall risk, comorbidities).

Fracture risk escalates with **the number and combination of risk factors**, often exceeding the risk associated with BMD loss alone. While BMD establishes the **diagnostic threshold**, the **therapeutic threshold** for treatment initiation should consider the full spectrum of these risks.

Age

- Fracture incidence rises **exponentially with age**, due not only to BMD reduction but also:
  - Declines in bone quality
  - Increased fall frequency
  - Slower neuromuscular protective responses
- **Older adults have a higher fracture risk** than younger individuals at the same BMD level.

Family History of Fragility Fractures

- A **positive family history**, particularly of **hip fractures**, is a **strong, independent predictor** of osteoporotic fractures.
- Genetic predisposition may influence both bone strength and fall susceptibility.

Previous Fragility Fractures

- History of non-traumatic fractures strongly predicts future fractures, **regardless of BMD**.
- Highest risk is associated with:
  - **Multiple vertebral fractures** (≥3)
  - **Hip, wrist, and humerus fractures**
- Even **mild vertebral fractures** significantly increase the likelihood of future vertebral injuries.

Bone Mineral Density (BMD)

- BMD reduction is a primary risk factor, reflecting both:
  - **Peak bone mass** (achieved in youth)
  - **Bone loss** (due to menopause, aging, disease, medications)
- **Each 1 SD decrease** in BMD increases fracture risk by **1.5–3 times**, especially at:
  - Femoral neck
  - Total hip
  - Lumbar spine

Smoking

- Smoking is an **independent risk factor** for both **vertebral** and **appendicular fractures**.
- It contributes to impaired bone formation and increased resorption.

Immobility

- Prolonged immobility moderately increases fracture risk by:
  - Reducing mechanical bone stimulation
  - Accelerating muscle loss (sarcopenia)

Comorbidities

- Multiple medical conditions contribute to osteoporosis by various mechanisms:
- **Chronic inflammation**
- **Hormonal imbalances**
- **Sarcopenia and fall risk**
- **Malabsorption syndromes**
- **Vitamin D deficiency**
- **Notable high-risk comorbidities include:**
- **Rheumatoid arthritis**
- **Inflammatory bowel disease**
- **Endocrinopathies** (e.g., hypogonadism, GH deficiency)
- **Organ transplantation**
- **COPD**
- **Type 1 and 2 diabetes mellitus**
- **Neurological/motor disorders** (e.g., Parkinson's disease, stroke, spinal cord injury)

Risk Factors for Falls

- Falls are the **primary proximate cause** of osteoporotic fractures in the elderly. Key contributors include:
- **Sensory impairments** (hearing, vision loss)
- **Neuromuscular disorders**
- **Cognitive impairment** (e.g., dementia)
- **Substance use** (alcohol)
- **Nutritional deficits**, particularly **vitamin D deficiency**
- **Environmental hazards**, such as slippery floors, poor lighting, and unsecured carpets, further exacerbate fall risk and must be addressed during prevention efforts.

METHODS FOR DIAGNOSIS OF OSTEOPOROSIS

The diagnosis of osteoporosis and assessment of fragility fracture risk involve a comprehensive approach that includes detailed case history, physical examination, and targeted laboratory and imaging investigations. A thorough case history should capture key information regarding the patient's medical background, lifestyle behaviours, and recognized osteoporosis risk factors. Particular emphasis should be placed on any history of low-impact or fragility fractures, as well as a family history, especially parental femur fractures, which significantly heighten the individual's risk for future hip and other osteoporotic fractures. Evaluation of comorbid conditions and review of medications that may affect bone metabolism (e.g., corticosteroids, anticonvulsants, aromatase inhibitors) are essential. In women, a detailed gynaecological history, including the age of menopause onset, provides additional insight into hormonal influences on bone health. The physical examination should focus on postural evaluation, identifying clinical signs such as exaggerated thoracic kyphosis or measurable height loss, which may suggest underlying vertebral compression fractures. Together, these elements form the foundation for selecting appropriate diagnostic imaging and laboratory assessments to confirm osteoporosis and guide treatment decisions.

ASSESSMENT OF FRACTURE RISK IN OSTEOPOROSIS

Integrated Risk Evaluation Approach

Accurate fracture risk assessment requires more than evaluating **bone mineral density (BMD)** alone. Modern clinical practice now incorporates **BMD-independent risk factors** using **validated algorithms** to estimate the **absolute risk of fragility fractures** over a medium-term period (typically 5–10 years). This integrative approach supports personalized treatment decisions and helps identify patients who will benefit most from **pharmacological interventions**.

Fracture Risk Algorithms

Several **mathematical models** have been developed to predict **10-year probabilities** of osteoporotic fractures by combining:

- **BMD measurements** (usually femoral neck via DXA)
- **Clinical risk factors (CRFs)** that are partially or entirely independent of BMD

The most widely used algorithm is the **FRAX® tool**, endorsed by the WHO, which integrates multiple variables to estimate:

- **10-year risk of a major osteoporotic fracture** (hip, spine, forearm, or humerus)
- **10-year risk of hip fracture specifically**

Key Clinical Risk Factors (CRFs) Incorporated in Algorithms

These factors have been validated in multiple cohort studies and meta-analyses for their **predictive power** and **ease of clinical identification**:

- **Age**
- **Sex**
- **Low body mass index (BMI)**
- **Prior fragility fracture**
- **Parental history of hip fracture**
- **Current smoking**
- **Glucocorticoid use**
- **Alcohol intake (≥3 units/day)**
- **Rheumatoid arthritis**
- **Secondary osteoporosis** (including diabetes, malabsorption, hyperthyroidism, etc.)
- **Femoral neck BMD** (optional but enhances accuracy)

Special Consideration of High-Impact Risk Factors

Certain conditions and therapies, though not always included in all standard algorithms, are now **increasingly prioritized in clinical decision-making** and even in drug reimbursement policies:

- **Type 1 and 2 diabetes mellitus**
- **Androgen deprivation therapy** (e.g., for prostate cancer)
- **Aromatase inhibitor therapy** (e.g., in breast cancer)

  These contribute to fracture risk **independent of BMD** and are frequently under-recognized.

Clinical Implications: Diagnostic vs. Therapeutic Thresholds

- **Diagnostic threshold**: Typically based on BMD (e.g., T-score ≤ -2.5 indicates osteoporosis)
- **Therapeutic threshold**: Determined by **absolute fracture risk**, not BMD alone. Patients with **moderate BMD but high clinical risk** may still require pharmacological treatment.

COMPREHENSIVE METHODS FOR DIAGNOSIS AND FRACTURE RISK ASSESSMENT IN OSTEOPOROSIS

The diagnosis of osteoporosis and evaluation of fragility fracture risk rely on a multidimensional approach that includes clinical history, physical examination, laboratory and imaging assessments, as well as validated risk prediction algorithms.

1. Clinical Assessment

A. A thorough **case history** is essential, focusing on:

- **Personal history of fragility fractures**, particularly low-impact fractures.
- **Family history**, especially parental hip fractures, significantly elevates the offspring's risk of hip and other osteoporotic fractures.
- **Comorbidities** known to affect bone metabolism (e.g., rheumatoid arthritis, diabetes).
- **Medications** with bone-depleting effects such as corticosteroids, androgen deprivation therapy, or aromatase inhibitors.
- **Gynecologic and menopausal history** in women, including the age of menopause onset.

B. A **physical examination** should include:

- Assessment of **height loss** or **thoracic kyphosis**, suggesting vertebral deformities or compression fractures.
- Evaluation of general posture and musculoskeletal health.

2. Laboratory Investigations

Laboratory testing may be indicated to identify:

- **Secondary causes** of osteoporosis (e.g., hyperparathyroidism, vitamin D deficiency).
- **Markers of bone turnover** in certain clinical situations.

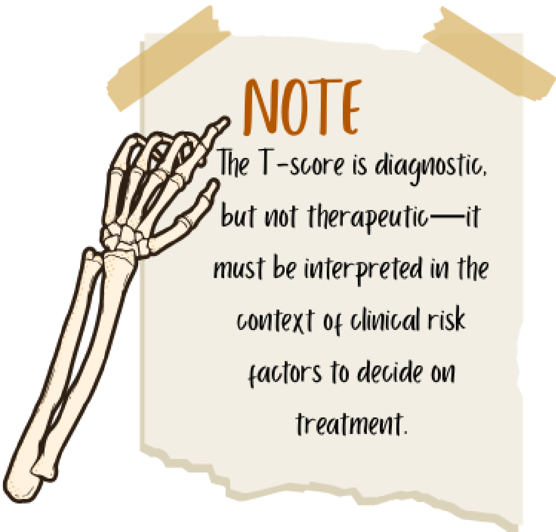
3. Diagnostic Imaging

Imaging is central to confirming the diagnosis and assessing fracture risk.

A. Bone Mineral Density (BMD) via Dual-energy X-ray Absorptiometry (DXA)

DXA is the gold standard for BMD assessment, measuring bone density at key fracture-prone sites lumbar spine (L1–L4), total hip, and femoral neck. The **lowest T-score** among these is used for diagnosis.

<u>WHO Classification based on T-score:</u>



- **Normal:**
  T-score between +2.5 and −1.0
- **Osteopenia:**
  T-score between −1.0 and −2.5
- **Osteoporosis:**
  T-score ≤ −2.5
- **Severe Osteoporosis:**
  T-score ≤ −2.5 with at least one fragility fracture

B. Special Considerations in DXA Interpretation

- **Spinal DXA** may be less reliable after age 65 due to **osteophytes, aortic calcifications, or fractures**; in such cases, **femoral DXA** is preferred.
- **Peripheral DXA** (e.g., forearm) is reserved for patients who are obese, have hyperparathyroidism, or cannot undergo spine/femur scans.

4. Advanced Imaging Tools and Software

A. Trabecular Bone Score (TBS)

TBS is an FDA-approved software tool applied to DXA images that assesses **trabecular microarchitecture**. It improves fracture risk prediction, especially in patients with **normal or osteopenic BMD**, and provides insight into **bone quality** beyond density.

B. Hip Structural Analysis (HSA)

Included in advanced DXA software, HSA calculates biomechanical parameters of the proximal femur, such as:

- **Cross-sectional area**
- **Cross-sectional moment of inertia**
- **Buckling ratio**

These parameters reflect the **mechanical strength and structural integrity** of bone and are useful for individualized fracture risk assessment.

5. Quantitative Computed Tomography (QCT) and Ultrasound

- **QCT**: Offers **volumetric BMD** and distinguishes between trabecular and cortical bone, but involves higher radiation and cost.
- **Quantitative Ultrasound (QUS)**: Radiation-free and portable, used mainly for **screening**, though less precise than DXA.

6. Conventional Radiography

Plain X-rays can identify **vertebral fractures**, a hallmark of osteoporosis, even in patients with normal BMD. Radiographs may also reveal signs of spinal deformity or other underlying pathology.

7. Fracture Risk Algorithms

To enhance fracture risk stratification, several **mathematical algorithms** integrate BMD with **clinical risk factors**, including:

- **FRAX®** (Fracture Risk Assessment Tool)
- **Garvan Fracture Risk Calculator**

These tools estimate a patient's **10-year probability of hip or major osteoporotic fractures**, even in those without DXA-confirmed osteoporosis. Factors considered include:

- Age and sex
- BMD (if available)
- Prior fractures
- Parental hip fracture
- Smoking, alcohol use
- Glucocorticoid use
- Secondary osteoporosis

Such models guide **clinical decision-making** and **reimbursement eligibility** for pharmacologic therapy.

BONE ULTRASOUND (QUANTITATIVE ULTRASOUND - QUS)

Bone ultrasound (QUS) is a non-invasive technique used to evaluate bone mass and structural integrity. It measures two key parameters: **speed** and **attenuation**, which are indirect indices of bone health. These measurements are most commonly taken at two sites: the **phalanges of the hand** and the **calcaneus** (heel bone).

Key Points

- **QUS vs DXA**:
  Ultrasound parameters for predicting osteoporotic fractures (vertebral and femoral) are comparable to DXA (Dual-energy X-ray Absorptiometry) in postmenopausal women and men.

However, QUS does not directly measure bone density, which means it can't be used for an official osteoporosis diagnosis (WHO criteria: T-score < −2.5 SD).

- **Predicting Fracture Risk**:
  While QUS is not a direct measure of bone density, it independently predicts the risk of fractures, and the results can vary from DXA due to other factors affecting bone structure.

Limitations

- **Device Variability**:
  The results may differ between devices, which can impact consistency.
- **Not a Diagnostic Tool**:
  QUS can't diagnose osteoporosis on its own because it doesn't directly measure bone mineral density.

Advantages

- **Low Cost and Portability**:
  QUS is cost-effective and portable, making it useful for initial screenings, especially in settings where DXA is unavailable.
- **No Radiation**:
  It doesn't involve radiation, making it a safer alternative for certain populations.

Clinical Use

- A **low QUS value**, combined with other clinical risk factors, may suggest the need for therapeutic intervention.
- A **high QUS value**, especially when there are no other risk factors, suggests a low probability of osteoporotic fractures, possibly eliminating the need for further testing.

In summary, while QUS is not a replacement for DXA in diagnosing osteoporosis, it serves as a valuable screening tool and can guide clinical decisions in assessing fracture risk, particularly in situations where DXA is not feasible.

CONVENTIONAL RADIOLOGY IN OSTEOPOROSIS FRACTURE DIAGNOSIS

Traditional radiology plays a critical role in diagnosing osteoporosis-related fractures, especially in the commonly affected sites: **spine, ribs, pelvis, proximal femur, proximal humerus, distal radius**, and **calcaneus**. Radiological techniques, along with vertebral morphometry (both semi-quantitative and quantitative), are used to identify and classify vertebral deformities, distinguishing them from vertebral fractures caused by bone fragility.

Types of Vertebral Fractures

Radiological studies help identify three primary types of vertebral fractures, based on spinal height reduction:

- **Wedge-shaped (anterior)**:
  The front part of the vertebra collapses, creating a wedge-like shape.
- **Biconcave (middle)**:
  The vertebra collapses inwards, resembling a biconcave shape.
- **Total vertebral collapse**:
  The entire vertebral body collapses, leading to significant height reduction.

Methods for Identifying Vertebral Deformities

There are two main classes of methods to assess vertebral deformities:

1. **Semi-Quantitative (SQ) Visual Methods**:
   - These methods involve visual evaluation of spine images for a differential diagnosis of vertebral deformities.
   - The **Genant criteria** are commonly used for grading vertebral fractures, which are classified as:
     - **Mild**
     - **Moderate**
     - **Severe**
   - These visual gradations help in assessing the severity of osteoporotic vertebral fractures.
2. **Quantitative Morphometric Methods**:
   - These methods provide more precise and quantitative analyses of spine deformity. They use measurements to assess the degree of vertebral height loss and deformation, offering a more objective approach than visual grading.

Clinical Significance

- **X-ray studies** are crucial in diagnosing osteoporosis fractures, particularly in the spine, where fractures may not always manifest as typical vertebral fractures.
- The **semi-quantitative visual methods** offer a faster, albeit less precise, assessment, while **quantitative methods** allow for a more detailed and accurate evaluation of vertebral deformities, supporting the clinical decision-making process for osteoporosis management.

In summary, conventional radiology is essential in identifying osteoporotic fractures, especially through methods like **Genant criteria** and quantitative vertebral morphometry, providing valuable insights into fracture severity and assisting in the diagnosis of osteoporosis-related fractures.

VERTEBRAL MORPHOMETRY IN OSTEOPOROSIS FRACTURE DIAGNOSIS

Vertebral morphometry is a quantitative method used to diagnose and assess vertebral fractures by measuring vertebral height. This technique is commonly applied to **lateral**

projection images of the **thoraco-lumbar spine**, which can be obtained through **conventional radiology (MRX)** or **DXA (MXA)**. It utilizes **VFA software** (vertebral fracture assessment) to analyze the images.

Key Features

- **Radiation Dose**: The technique involves low radiation exposure (50 µSv), which is approximately 1/100th of the dose used in conventional radiography, making it a safer alternative.
- **Image Coverage**: VFA software allows for the capture of the entire dorsal and lumbar spine in a single image, focusing on vertebral body height measurements from **T4–L4** (the thoracic to lumbar region).
- **Quantitative Measurement**: Vertebral morphometry quantitatively assesses the vertebral height, providing precise measurements for better diagnosis and monitoring.

Applications

- **Fracture Severity Assessment**: Vertebral morphometry is used to evaluate the **severity of vertebral fractures** identified using **semi-quantitative (SQ)** methods (such as the Genant criteria).
- **Follow-Up**: It helps monitor **new fractures** or the **progression of preexisting fractures** during patient follow-up. This is particularly important for tracking the evolution of osteoporotic fractures over time.

Limitations

- **Qualitative X-ray Analysis Requirement**: Vertebral morphometry cannot be performed in isolation. A previous **qualitative X-ray analysis** is required to rule out vertebral deformities caused by factors other than osteoporosis, ensuring that the results are specific to osteoporotic fractures.

Vertebral morphometry is an effective tool for quantitatively assessing vertebral fractures and monitoring changes in spine health over time. By combining it with **semi-quantitative methods** and **X-ray analysis**, healthcare providers can gain a comprehensive understanding of vertebral deformities, making it an important technique for both initial diagnosis and ongoing patient management.

SPINAL MRI (MAGNETIC RESONANCE IMAGING)

MRI is highly effective for diagnosing vertebral fragility fractures, especially when multiple vertebrae are involved. It provides detailed imaging that can differentiate between recent and older fractures and identify signs of impending structural failure.

Key Features

- **Signal Changes in T2 and STIR Sequences**: MRI detects changes in **T2** and **STIR (Short Tau Inversion Recovery)** sequences, which help identify **bone oedema,** a sign of recent fracture activity.
- **Differentiating Fractures**: MRI can distinguish **recent fractures** from **older ones** based on the presence of bone oedema, which is more prominent in acute fractures.
- **Predicting Future Fractures**: MRI can identify vertebrae that have not yet deformed but are showing early signs of impending fracture, aiding in preventive care.

SPINAL CT (COMPUTED TOMOGRAPHY)

CT is primarily used to assess the bone structure of vertebrae in more detail, particularly in cases of traumatic fractures where there may be complex bone involvement.

Key Features

- **Detailed Bone Assessment**: CT provides high-resolution images that help evaluate the bone components of a fractured vertebra, identifying any potential displacement or dislocation of bone fragments into the **medullary canal** (bone marrow).
- **Not Routine for Osteoporosis**: While CT is not typically used in routine osteoporosis evaluations, it can be a valuable complement to MRI in certain situations where detailed bone analysis is necessary.

Clinical Use

- **MRI** is preferred for detecting and monitoring **vertebral fragility fractures**, especially when multiple vertebrae are affected. It helps in identifying recent fractures and assessing the risk of future fractures.
- **CT** is more suitable for **traumatic fractures** with complex bone displacements, but is not used routinely for osteoporosis diagnosis. It may be indicated alongside MRI for detailed evaluation of specific cases.

LABORATORY TESTS FOR THE DIAGNOSIS OF OSTEOPOROSIS

Osteoporosis diagnosis and evaluation include two levels of laboratory testing to assess bone health, rule out secondary causes, and guide appropriate treatment. These tests help distinguish **primary osteoporosis** from **secondary causes** involving metabolic, endocrine, or systemic disorders.

1. **Level I Laboratory Tests (First-Line Screening)**

These are **routine baseline investigations** essential for evaluating bone metabolism and ruling out common secondary causes.

Included Tests:

- **Erythrocyte Sedimentation Rate (ESR)**: Screens for underlying inflammatory or chronic systemic diseases.
- **Complete Blood Count (CBC)**: Helps detect anaemia or hematologic disorders.
- **Total Protein and Protein Electrophoresis:** Identifies monoclonal gammopathies (e.g., multiple myeloma).
- **Serum Calcium:** Assesses calcium metabolism.
- **Phosphoremia (Serum Phosphate):** Evaluates phosphate levels, important in bone mineralization.
- **Total Alkaline Phosphatase (ALP):** Marker of bone turnover; elevated in high bone remodelling states.
- **Serum Creatinine (Creatininemia):** Evaluates renal function, essential before initiating certain osteoporosis treatments.
- **24-Hour Urinary Calcium:** Assesses calcium excretion; helps detect hypercalciuria or calcium-wasting disorders.

<u>**Clinical Utility:**</u>

- If all **Level I tests are normal**, they **exclude secondary osteoporosis in ~90%** of cases, confirming likely **primary osteoporosis**.

2. **Level II Laboratory Tests (Second-Line/Targeted Investigations)**

These are **advanced or specialized tests** performed when secondary osteoporosis is suspected based on clinical history or abnormal first-line results.

Included Tests:

- **Ionized Calcium:** More accurate reflection of biologically active calcium.
- **Thyroid Stimulating Hormone (TSH):** Evaluates for hyperthyroidism—a known secondary cause.
- **Parathyroid Hormone (PTH):** Detects hyperparathyroidism, a major contributor to bone loss.
- **25-OH-Vitamin D:** Assesses vitamin D status; deficiency is common and correctable.
- **Overnight Dexamethasone Suppression Test (1 mg Cortisol):** Screens for Cushing's syndrome.
- **Free Androgen Index (in males):** Detects hypogonadism, which can contribute to osteoporosis.
- **Serum and Urine Immunofixation**:

Identifies monoclonal proteins associated with multiple myeloma.

- **Anti-transglutaminase Antibodies**: Screens for celiac disease, which affects nutrient absorption and bone health.
- **Other Disease-Specific Tests**:
  - **Ferritin and Transferrin Saturation**: Rule out hemochromatosis.
  - **Tryptase**: Associated with systemic mastocytosis.

Clinical Utility

- Level II tests are **selected based on individual clinical context** (e.g., symptoms, history).
- They **identify secondary causes** such as **endocrine disorders, malignancies, malabsorption, or chronic inflammation**.

Summary Table

LEVEL	TEST	PURPOSE
Level 1	ESR, CBC, Total protein, Serum Ca, Phosphorus, ALP, Creatinine, 24-hr urine Ca	Screen for common metabolic abnormalities
Level 2	Ionized Ca, TSH, PTH, 25-OH-D, Cortisol (DST), Free Androgen Index, Immunofixation, Anti-TTG, Ferritin, Tryptase	Detect specific secondary causes based on clinical suspicion

BONE TURNOVER MARKERS

Bone turnover markers are mainly used to obtain information about the extent of new-bone formation and resorption processes. They are overall indicators of skeletal remodelling, and, therefore, vary considerably at the analytical and biological level; therefore, there is no indication for their use in routine evaluations of individual patients. In population studies, especially in postmenopausal women, they may prove useful when seeking to estimate the risk of fracture, irrespective of BMD. They have also been widely used in clinical trials aimed at monitoring the efficacy and mechanism of action of new drugs.

Those commonly used in the assessment of bone neoformation are osteocalcin, bone isoenzyme of alkaline phosphatase (B-ALP), and type I collagen propeptides (PINP and PICP), while the most common markers of resorption are urinary pyridinoline (PYR), urinary deoxypyridinoline (DPYR), and serum levels of type I collagen telopeptides. Their significant alteration makes it possible to orient diagnosis towards primary or secondary diseases typical of the skeleton (Paget's disease of bone, osteomalacia, hypophosphatasia, bone metastases, etc.). Because it is possible to find significant changes in markers after a few weeks of beginning the treatment, it has been proposed that they can also be used to evaluate patient adherence to drug treatment. [12, Rank 1]

PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS

The primary goal of osteoporosis treatment is to reduce the risk of fractures, particularly in individuals identified as high risk. Importantly, the T-score values obtained from DXA scans, though used by the World Health Organization (WHO) to define osteoporosis, are not sufficient alone to determine when to begin pharmacological treatment. Instead, fracture risk should be assessed through a comprehensive approach that includes bone mineral density (BMD) as well as clinical risk factors such as age, chronic steroid use, low body weight, smoking, and personal history of fractures.

To guide treatment decisions, validated tools such as the FRAX algorithm are used to calculate a patient's 10-year probability of sustaining a major osteoporotic or hip fracture. These tools are especially helpful in patients who have not yet experienced a fracture, allowing clinicians to intervene before the first event occurs.

Some clinical conditions carry such a high fracture risk that treatment should begin without delay or even the need for DXA testing. These include a history of previous osteoporotic fractures, long-term glucocorticoid use (e.g., prednisone ≥5 mg/day), and patients undergoing hormone-blocking therapy for cancer, such as androgen deprivation in men with prostate cancer or aromatase inhibitors in women with breast cancer. In such cases, immediate pharmacologic intervention is often warranted to prevent further skeletal complications.

ANTI-OSTEOPOROTIC DRUGS

Pharmacological treatments for osteoporosis are broadly categorized into two main groups:

1. **Anti-resorptive (Anti-catabolic) agents**
2. **Anabolic agents**

Both classes have demonstrated significant efficacy in **reducing vertebral fracture risk**. However, their ability to **lower the incidence of non-vertebral and femoral fractures** is supported by evidence only for select agents.

- Drugs such as **denosumab**, **strontium ranelate**, and **teriparatide** have shown broader efficacy but require a **specialist-approved Treatment Plan** as per regulatory guidelines.
- Optimal outcomes depend not only on drug efficacy but also on **patient adherence**, which necessitates:
    - Clear communication of the **benefits and potential risks**,

Individualized drug selection based on patient characteristics, risk profile, and tolerability,
  - Regular **monitoring and follow-up**.

Effective osteoporosis management hinges on a **comprehensive, patient-centred approach** that integrates pharmacological therapy with lifestyle and nutritional interventions.

ANTI-CATABOLIC DRUGS: BISPHOSPHONATES (BPS)

Bisphosphonates are synthetic analogs of pyrophosphate that selectively bind to bone surfaces undergoing active remodelling. Their primary mechanism is the **inhibition of osteoclast-mediated bone resorption**, leading to reduced bone turnover and increased bone mineral density (BMD). The specific anti-resorptive mechanism varies depending on the **presence or absence of an amino group** in their molecular structure.

Pharmacokinetics and Contraindications

- Oral bioavailability is **low (0.5–5%)**, and absorption is significantly affected by food and beverages.
- Bisphosphonates are **contraindicated** in:
  - **Hypocalcaemia**
  - **Gastrointestinal disorders** (e.g., oeso - phageal stricture, gastritis)
  - **Renal impairment** (Creatinine clearance <30 mL/min)
  - **Pregnancy and lactation**

Types and Clinical Use of Bisphosphonates

Non-Aminobisphosphonates:

- **Etidronate** and **Clodronate**:
  - Lack nitrogen-containing side chains.
  - Etidronate: Increases vertebral BMD but is **not recommended for osteoporosis**.
  - Clodronate: Shown to reduce fracture risk at **800 mg/day orally**, but **intramuscular formulations** (100 mg/week or 200 mg biweekly) lack strong fracture-prevention evidence, making it a **second-line option**.

Aminobisphosphonates:

- **Alendronate** and **Risedronate**:
  - Demonstrated robust efficacy in **reducing vertebral, non-vertebral, and hip fractures**.
  - Dosing:
    - Alendronate: 70 mg weekly or 10 mg daily; **liquid formulations now available**.
    - Risedronate: 35 mg weekly, 75 mg on two consecutive days/month, or 5 mg daily.
  - Registered for **male osteoporosis** and **glucocorticoid-induced osteoporosis**.
- **Ibandronate:**
  - Oral dose: 2.5 mg/day (effective for **vertebral fractures only**).

- Marketed as: 150 mg/month orally or 3 mg IV every 3 months.
- Efficacy in preventing **non-vertebral or hip fractures** is limited.

- **Zoledronic Acid:**
  - Potent intravenous bisphosphonate administered as **5 mg IV once yearly**.
  - Proven to significantly reduce **vertebral, non-vertebral, and hip fractures**.
  - A notable **reduction in all-cause mortality** was observed in an ancillary study.
  - Approved for use in **men** and **corticosteroid-induced osteoporosis**.
- **Neridronate:**
  - Only bisphosphonate approved for **osteogenesis imperfecta**.
  - Also indicated for **complex regional pain syndrome type I (algodystrophy)** based on high-level evidence from a randomized controlled trial.

KEY TAKEAWAYS

- First-line bisphosphonates for osteoporosis: Alendronate, Risedronate, Zoledronic acid.
- Special indications: Neridronate for osteogenesis imperfecta; Zoledronic acid for broader fracture protection and mortality benefit.
- Patient education, correct administration timing (e.g., fasting state, upright position), and monitoring renal function are essential to maximize efficacy and minimize adverse effects.

DENOSUMAB: ANTI-RESORPTIVE AGENT

Denosumab is a fully human **monoclonal antibody** that targets **RANKL (Receptor Activator of Nuclear Factor-κB Ligand)**, a key mediator of osteoclast formation, function, and survival. By inhibiting RANKL, denosumab **suppresses bone resorption**, effectively reducing bone turnover

Dosing and Efficacy

- **Standard dose:**
  60 mg **subcutaneously every 6 months**.
- This regimen achieves **near-complete suppression of bone turnover** and results in:
  - **Superior increases in bone mineral density (BMD)** in both **trabecular and cortical bone** compared to bisphosphonates.
  - **Significant reduction in fragility fractures** at **all major skeletal sites**, including spine, hip, and non-vertebral sites

Special Clinical Indications

- Effective in **postmenopausal women** with osteoporosis.
- Used to prevent fractures in:
  - **Women with breast cancer** receiving **aromatase inhibitors**.

- **Men with prostate cancer** undergoing **androgen deprivation therapy (ADT)**.

Combination and Sequential Therapy

- In **severe osteoporosis**, combination therapy with **denosumab and teriparatide** has shown **synergistic effects** on BMD.
- **Sequential therapy** (teriparatide followed by denosumab) also results in **greater BMD gains** than monotherapy.

Discontinuation Concerns

- **Key distinction from bisphosphonates**:
  - Denosumab's effects **recede rapidly after discontinuation**, leading to:
    - **Abrupt increase in bone turnover**.
    - **Accelerated bone loss**.
    - Increased risk of **rebound vertebral fractures**.
- **Clinical recommendation:**
  Upon discontinuing denosumab, patients should be transitioned **promptly to a bisphosphonate** to preserve bone mass

Safety and Monitoring

- **Hypocalcaemia** is a potential adverse effect; therefore:
  - **Calcium and vitamin D levels must be optimized** before initiation.
  - **Adequate supplementation** should continue throughout treatment.

TERIPARATIDE: AN ANABOLIC AGENT FOR OSTEOPOROSIS

Teriparatide is a recombinant form of the **active 1–34 amino acid fragment of human parathyroid hormone (PTH)**. Unlike anti-resorptive agents, teriparatide **stimulates new bone formation**, making it the primary anabolic treatment option for osteoporosis.

Mechanism of Action

- **Intermittent subcutaneous administ - ration** of teriparatide preferentially stimulates **osteoblastic activity**, leading to **net bone formation**.
- This occurs during the so-called **"anabolic window"**, particularly pronounced in the **first 12 months** of therapy.
- Although it stimulates both formation and resorption, the **formation dominates**, especially in early treatment phases.

Efficacy

- **Dose**: 20 μg **subcutaneously once daily**.
- Significantly increases **trabecular BMD**, particularly at the **lumbar spine** (approx. **10% increase at 18 months**).
- Also improves **cortical bone geometry**, enhancing **bone strength and resistance to fracture**.
- Proven to **reduce both vertebral and non-vertebral fractures** in **postmenopausal women with severe osteoporosis**.

Duration and Post-Treatment Considerations

- **Maximum recommended treatment duration: 24 months (lifetime exposure).**
- **Post-treatment**: Rapid loss of BMD may occur upon discontinuation.
    - **Recommendation**: Initiate **anti-resorptive therapy** (e.g., bisphosphonates or denosumab) immediately after stopping teriparatide to **preserve bone gains**.

Adverse Effects

- Generally well-tolerated, but may be associated with:
    - **Mild nausea**
    - **Leg cramps**
    - **Asymptomatic hypercalcemia** (transient and dose-dependent)

Contraindications

Teriparatide should **not be used** in individuals with:

- **Pre-existing hyperparathyroidism**
- **Paget's disease of bone**
- **Severe renal impairment**
- **History of skeletal malignancies or bone metastases**
- **Prior skeletal radiation therapy**

Clinical Pearls

- Best suited for **patients with very high fracture risk**, such as those with:
    - **Multiple fragility fractures**
    - **Very low BMD (T-score ≤ –3.5)**
    - **Glucocorticoid-induced osteoporosis not responding to anti-resorptives**
- Can be part of **sequential therapy**, followed by anti-resorptive agents to maintain long-term benefits.

STRONTIUM RANELATE: A DUAL-ACTION BONE AGENT

Strontium ranelate exhibits a **dual mechanism of action**, making it unique among osteoporosis treatments. It simultaneously:

- **Stimulates bone formation** (increased osteoblast activity)
- **Reduces bone resorption** (inhibition of osteoclast differentiation and activity)

This balanced effect contributes to improved bone mass and reduced fracture risk.

Efficacy

- Demonstrated to significantly **reduce the risk of vertebral, non-vertebral, and hip fractures** in **postmenopausal women with osteoporosis**.
- Also approved for use in **adult men with severe osteoporosis** at high fracture risk when other therapies are unsuitable.
- Bone mineral density (BMD) gains observed during therapy are **partially (~50%)**

attributed to strontium's higher atomic mass compared to calcium, thus inflating DXA scan readings.

Mechanism Highlights

- **Anabolic effect**: Enhances markers of **bone formation**.
- **Anti-resorptive effect**: Slightly decreases **markers of bone resorption**.
- Classified as a **"dual-action bone agent"** due to this combined pharmacologic profile.

Safety and Contraindications

Despite its efficacy, strontium ranelate has **serious cardiovascular and hypersensitivity risks**:

Contraindicated in:

- **Current or past history** of:
  - **Ischemic heart disease**
  - **Peripheral arterial disease**
  - **Cerebrovascular disease**
  - **Uncontrolled hypertension**

Adverse Events:

- **Increased risk of myocardial infarction and venous thromboembolism**
- Rare but serious **hypersensitivity reactions**, including:
  - **DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)**
  - **Stevens-Johnson syndrome**
  - **Toxic epidermal necrolysis**

Regulatory and Clinical Use

- Due to the above risks, **regulatory agencies restrict its use** to:
  - **Postmenopausal women** and **adult men with severe osteoporosis**
  - Who are at **high risk of fracture**
  - And for whom **other approved osteoporosis treatments are unsuitable or contraindicated**

Clinical Considerations

- Patients must undergo **cardiovascular risk assessment** before initiation.
- Regular monitoring of **blood pressure, cardiovascular status, and hypersensitivity symptoms** is essential during treatment.
- Not typically considered a first-line therapy due to safety concerns.

HORMONE REPLACEMENT THERAPY (HRT) IN OSTEOPOROSIS

Hormone Replacement Therapy (HRT), including **oestrogen alone**, **oestrogen-progestin combinations**, and **tibolone**, has been shown to positively impact bone health in **postmenopausal women**.

Mechanism of Action

- **Reduces bone turnover** by suppressing osteoclast activity.

- **Increases bone mass**, particularly in trabecular bone.

Efficacy

- Proven **anti-fracture efficacy** in multiple **randomized controlled trials** and **large-scale observational studies**.
- HRT also **reduces the risk of colorectal cancer**, adding a secondary preventive benefit.

Risks and Limitations

Despite its effectiveness, HRT use is **limited by significant health risks**:

- **Increased risk of breast cancer**
- **Elevated risk of thromboembolic events**
- **Higher incidence of stroke**

These adverse effects have led to **withdrawal of the recommendation** for using HRT as a primary treatment or prevention method for osteoporosis.

Current Clinical Role

- HRT is **no longer routinely recommended** for osteoporosis prevention or treatment.
- **However**, in selected women:
  - **Experiencing climacteric (menopausal) symptoms**
  - **Aged 50–55 years**
  - With **low cardiovascular and breast cancer risk**
  - A **short-term course of oestrogen therapy** (or **oestrogen + progestin**, if the uterus is intact) may be:
  - Considered **physiologically appropriate**
  - **Effective in alleviating vasomotor symptoms** and **contributing to osteoporosis prevention**

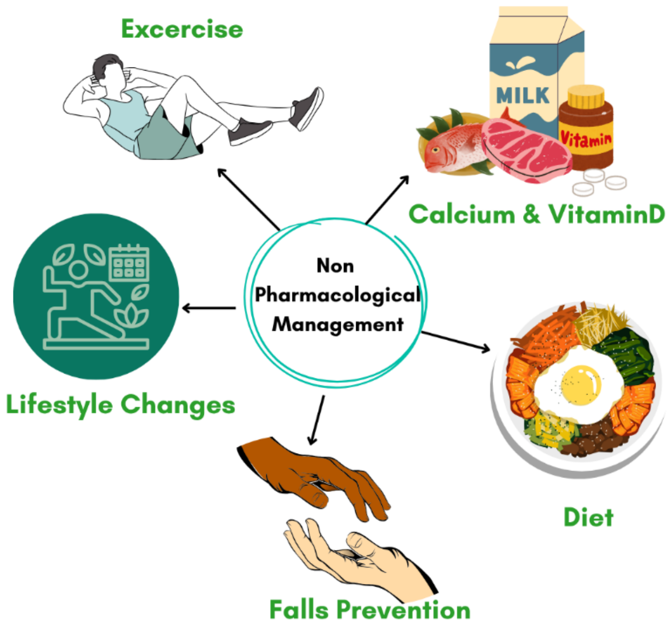
Clinical Considerations

- Careful **individual risk-benefit assessment** is critical before initiating HRT.
- The **lowest effective dose** for the **shortest possible duration** is advised.
- HRT should be prescribed primarily for **symptom relief**, not solely for bone protection.

NON-PHARMACOLOGIC MANAGEMENT AND PREVENTION OF OSTEOPOROSIS

Osteoporosis prevention involves proactive strategies to delay or prevent the onset of bone loss. In contrast, treatment targets individuals already diagnosed with osteoporosis, regardless of the presence of fractures, especially those at elevated risk for initial or recurrent fragility fractures.

Prevention is primarily centred around modifying risk factors and adopting **lifestyle measures** to maintain optimal bone health. These non-pharmacological approaches are essential both in preventive care and as adjuncts to pharmacologic treatment.



Key Non-Pharmacologic Strategies

1. **Lifestyle Modifications:**
   a. **Smoking cessation:** Smoking accelerates bone loss and reduces calcium absorption.
   b. **Limiting alcohol intake:** Excessive alcohol consumption impairs bone formation and increases fall risk.
2. **Nutrition:**
   a. **Adequate calcium and vitamin D intake:** Ensures proper bone mineralization.
   b. **Balanced diet rich in protein, fruits, and vegetables:** Supports bone remodelling and overall health.
3. **Physical Activity:**
   a. **Weight-bearing and resistance exercises:** Stimulate bone formation and improve muscle strength and balance, reducing fall risk.
   b. **Fall-prevention training (e.g., Tai Chi, balance exercises):** Enhances coordination and reduces the likelihood of injury.
4. **Environmental Modifications:**
   a. **Fall-proofing the living space:** Removing loose rugs, installing grab bars, and ensuring adequate lighting.
   b. **Use of assistive devices if needed:** Canes or walkers to enhance stability.
5. **Regular Monitoring and Education:**
   a. **Bone mineral density (BMD) testing:** For early identification of bone loss.
   b. **Patient education:** Emphasizing adherence to healthy habits and fall-prevention strategies.

NUTRITIONAL MANAGEMENT IN OSTEOPOROSIS

Calcium

Calcium plays a fundamental role in bone health across all life stages. Adequate calcium intake increases bone matrix density in children and adolescents, helps maintain bone mass in adults, and slows bone loss in postmenopausal women.

1. **Sources of Calcium:**

- **Primary sources:** Milk and dairy products.

- **Secondary sources:** Nuts (especially almonds), green leafy vegetables (such as cabbage, spinach, and turnips), and legumes.
- Despite these sources, **dietary calcium intake is often insufficient**, particularly among the elderly, contributing to **negative calcium balance** and potentially leading to **secondary hyperparathyroidism**.

2. **Daily Calcium Requirements:**

Calcium needs vary with **age, physiological states** (e.g., **pregnancy and lactation**), and health status. Supplementation is particularly important when dietary intake does not meet the recommended levels.

3. **Efficacy of Calcium Supplementation:**

- **Calcium supplementation alone** can modestly improve bone mineral density (BMD), especially in:
  - Women with inadequate dietary intake.
  - Women in the early postmenopausal period (within 5 years).
- **Fracture risk reduction** with calcium alone is limited; however, **calcium combined with vitamin D** has demonstrated greater **anti-fracture efficacy**.
- The benefits of supplementation are **greater in populations with frequent and severe deficiencies** of calcium and vitamin D.

4. **Risks and Safety Considerations:**

- **Calcium supplements** may slightly increase the risk of **non-oxalate kidney stones**.
- **Dietary calcium** is associated with a **lower risk** of stone formation than supplements.
- Concerns have been raised about **vascular calcification and cardiovascular risk** from supplemental calcium; although recent studies do **not confirm a strong link**, caution is advised.

5. **Clinical Recommendations for Calcium Supplementation:**

- **Assess dietary calcium intake** using a brief dietary questionnaire before prescribing supplements.
- **Prioritize food and mineral water** sources rich in calcium before initiating supplementation.
- Use **calcium supplements** only when necessary, aiming for:
  - The **lowest effective dose** to meet daily requirements.
  - **Divided doses** (e.g., 500 mg with lunch and 500 mg with dinner) to enhance absorption and minimize side effects.

VITAMIN D IN NUTRITIONAL MANAGEMENT

Vitamin D is essential for bone health, primarily supporting calcium absorption and bone mineralization. It is found mainly in animalbased foods, such as fatty fish, liver, milk, and dairy products, while its presence in plant-derived fats is negligible. Approximately 20% of circulating vitamin D comes from dietary intake, with the remaining majority synthesized endogenously in the skin via UVB exposure. This cutaneous synthesis significantly declines with age, making older adults particularly susceptible to deficiency and often requiring supplementation.

Role in Fracture Prevention and Bone Mineral Density (BMD)

Vitamin D supplementation, particularly as **cholecalciferol (D3)** or **ergocalciferol (D2)**, is modestly effective in improving BMD, most notably in the femur, and in reducing the incidence of **hip and non-vertebral fractures**. These effects are more pronounced when **combined with adequate calcium intake**, which is essential for optimizing bone health and therapeutic outcomes. Adequate levels of calcium and vitamin D are **prerequisites for pharmacologic treatment of osteoporosis**, as deficiencies are common causes of suboptimal therapeutic response. Additionally, vitamin D supplementation has been associated with a slight but statistically significant reduction in all-cause mortality in the elderly, although **extra-skeletal benefits remain unproven** despite plausible biological mechanisms.

Assessment and Monitoring

Serum **25-hydroxyvitamin D [25(OH)D]** is the most reliable indicator of vitamin D status. However, routine screening is **not recommended**, especially in elderly populations with high prevalence of deficiency, unless comorbidities or risk of severe hypercalcemia are present. When supplementation is within the **safe upper intake level (<4000 IU/day)**, routine 25(OH)D testing for monitoring is generally unnecessary.

If measurement is indicated, testing should occur after **3–6 months of supplementation** to evaluate steady-state levels and adjust dosing accordingly. The target serum concentration is **30–50 ng/mL (75–125 nmol/L)**.

Supplementation Strategy

Vitamin D deficiency is so prevalent in the elderly and individuals at risk for fragility fractures that supplementation is often indicated **without prior testing**. When dietary correction or safe sun exposure is not feasible, **daily or weekly oral cholecalciferol** is the preferred method of supplementation. Avoid **hydroxylated metabolites (e.g., calcitriol, alfacalcidol)** unless indicated, as they bypass endogenous regulatory pathways and pose a higher risk of **hypercalcemia**.

- **Daily supplementation** is physiologically preferable.

- **Weekly/monthly dosing** is acceptable for improving adherence.
- **Avoid high-dose boluses >100,000 IU**, as these may paradoxically increase fracture risk and bone resorption markers.

For **severe deficiency**, a **weekly dose of 50,000 IU for 2–3 months** may restore serum levels, followed by maintenance dosing of up to **2,000 IU/day** or equivalent.

Special Considerations for Hydroxylated Metabolites

Alternative vitamin D metabolites may be used in specific conditions:

- **Calcifediol [25(OH)D_3]**: Offers faster correction and may be preferred in:
    - Severe liver failure
    - Male hypogonadism
    - Inactivating mutations in 25-hydroxylase
    - Obesity and malabsorption syndromes
- **Calcitriol [1,25$(OH)_2D_3$]**: Indicated for:
    - Moderate-to-severe renal impairment
    - Hypoparathyroidism
    - Genetic defects in 1-α hydroxylase
    - Severe intestinal malabsorption

These agents can lead to **hypercalcemia and hypercalciuria**, requiring **regular serum and urinary calcium monitoring**. Even in these cases, **cholecalciferol should not be omitted** due to its autocrine/paracrine roles and potential systemic effects.

OTHER NUTRIENTS IN BONE AND MUSCLE HEALTH

Adequate intake of specific nutrients beyond calcium and vitamin D plays a crucial role in maintaining musculoskeletal health and preventing osteoporotic fractures. In particular, **increasing protein intake** in individuals with previously inadequate dietary protein has been shown to reduce the risk of **hip fractures** in both men and women. Protein is essential not only for maintaining **bone integrity** but also for supporting **muscle function** and recovery, particularly following osteoporotic fractures.

Recommended Protein Intake:

- **1.0–1.2 g/kg/day** of body weight
- Ideally, **20–25 g of protein per meal**
- This intake should be combined with **resistance training** (e.g., strength-building exercises), which synergistically enhances **muscle mass and strength**, key factors in fall and fracture prevention.

In addition to protein, several **micronutrients** also contribute to musculoskeletal health:

- **Zinc**: Important for bone formation and remodelling; acts as a cofactor for various enzymes involved in collagen synthesis.
- **Silicon**: Contributes to bone mineralization and collagen synthesis.
- **Vitamin K**: Plays a vital role in the carboxylation of osteocalcin, a protein essential for bone mineral binding.

- **Vitamin E**: Exhibits antioxidant properties, which may protect bone cells from oxidative stress and influence bone turnover.
- **Vitamin B6 and B12**: Involved in homocysteine metabolism; elevated homocysteine levels are associated with increased fracture risk.
- **Magnesium**: Contributes to bone structure and influences calcium metabolism and parathyroid hormone secretion.

Together, these nutrients support **bone strength**, **muscle function**, and **overall physical performance**, especially in older adults and those at risk for fragility fractures. Therefore, a **balanced diet** rich in these nutrients, along with adequate protein and regular exercise, should be emphasized in the management and prevention of osteoporosis.

THE IMPACT OF PHYSICAL ACTIVITY ON OSTEOPOROSIS

Physical activity plays a vital role in the prevention and management of osteoporosis. Even **short periods of immobilization** can result in significant loss of **bone mass**, emphasizing the importance of maintaining **regular physical activity** throughout life.

However, it is important to **balance physical activity**, especially in **young women**, as **excessive training or competitive sports** may lead to **hormonal imbalances** and **nutritional deficiencies**, which can be detrimental to bone health.

Types of Physical Activity

Physical activity relevant to bone health can be broadly classified into two categories:

1. **Aerobic Activity (Low or High Impact)**
    - Examples: **Jogging, soccer, basketball, volleyball, baseball, racket sports, gymnastics**
    - **Walking** is a common form, particularly suitable for older adults due to its **low impact**, **self-paced nature**, and **broad acceptability**. However, meta-analyses have shown **limited effects** of regular walking on **lumbar and femoral bone mineral density (BMD)**.
    - **High-intensity walking**, **intermittent jogging**, **stair climbing**, and **stepping** may help maintain or slightly improve BMD, particularly in **postmenopausal women**.
2. **Muscle-Strengthening Activity**
    - Examples: **Weightlifting, resistance training, bodyweight exercises, swimming, cycling, use of weights for static exercise**
    - These activities help improve **muscle mass**, **strength**, and **postural stability**, all of which contribute to a **reduced risk of falls and fractures**.

Multi-Component Training

Programs that integrate **moderate-to-high impact exercises**, **muscle-strengthening routines**, and **balance training** show the **most favorable outcomes** for BMD improvements at the **femur and lumbar spine**.

- **Vibration platform training** has shown **inconclusive results**, with no consistent evidence supporting improvements in BMD at critical sites such as the **femoral neck or spine**.

Epidemiological Evidence and Clinical Recommendations

- Observational studies indicate a **correlation** between physical activity and **reduced fracture risk**.
- In elderly or osteoporotic individuals, **exercise prescriptions** should be **individualized**, following a **thorough medical evaluation** to assess:
  - Muscle strength
  - Gait and balance
  - Cardiovascular function
  - Presence of comorbidities

Even **modest increases** in physical activity, such as walking **outdoors for at least 30 minutes per day**, are **encouraged**, not only to improve balance and **reduce fall risk** but also to potentially boost **serum vitaminD [25(OH)D]** levels through sunlight exposure.

Although evidence on direct benefits to bone mass may be limited, these activities are **low-risk and high-reward** for overall physical function and **fracture prevention** in older adults.

PREVENTION OF FALLS IN OLDER ADULTS

Falls are a **leading cause of fractures**, particularly **hip fractures**, in the elderly. Preventing falls is therefore a **critical component** in the management and prevention of osteoporosis-related complications.

Key Modifiable Risk Factors for Falls

Falls are often linked to a variety of modifiable risk factors, including:

- **Physical disabilities** (e.g., reduced mobility)
- **Balance disorders** and **gait instability**
- **Neuromuscular dysfunction**
- **Visual impairments**
- **Cardiovascular diseases** (e.g., orthostatic hypotension, arrhythmias)
- **History of previous falls**
- **Medications**, particularly **psychotropic agents**
- **Cognitive impairments** (e.g., dementia, delirium)
- **Environmental hazards**

Multidisciplinary interventions targeting these factors can significantly reduce fall risk.

Evidence-Based Fall Prevention Strategies

1. **Personalized Physical Activity Programs**
   - **Muscle-strengthening exercises, balance training,** and **gait rehabilitation** have shown to **reduce fall risk** by improving physical function and postural control.
   - Programs should be **tailored** to the individual's capabilities and comorbidities.
2. **Pharmacological Review**
   - A **critical review of current medications**, particularly aiming to **reduce or eliminate psychotropic drug use**, can positively impact fall risk.
3. **Vitamin D Supplementation**
   - Adequate levels of **vitamin D** help maintain **muscle strength** and **neuromuscular coordination**, thereby reducing fall risk.
   - Routine supplementation is recommended, especially in individuals with low sun exposure or confirmed deficiency.
4. **Patient and Caregiver Education**
   - Education on **risk factors** and **preventive behaviours**, especially regarding **in-home safety**, is essential.
   - Simple lifestyle modifications (e.g., rise slowly from a seated position, use handrails) can prevent many falls.
5. **Environmental Modifications**
   - Conducting a **home hazard assessment** can identify and mitigate risks such as:
     - Poor lighting
     - Loose rugs or exposed wires
     - Slippery floors
     - Inadequate footwear
     - Presence of pets in walkways
6. **Use of Hip Protectors**
   - **Hip protectors** (external padding or orthotic devices) may reduce the impact of falls on the hip.
   - However, current evidence shows **mixed benefits**.
   - Their use is currently **recommended primarily for institutionalized patients** with **very high fall risk**.

An effective fall prevention strategy should be **comprehensive and personalized**, incorporating:

- **Physical rehabilitation**
- **Medication optimization**
- **Nutritional support**
- **Education**
- **Environmental safety measures**

Implementing these interventions can **significantly lower fracture incidence**, especially in high-risk elderly populations.

INTEGRATED APPROACHES FOR SECONDARY PREVENTION OF FRAGILITY FRACTURES

Secondary prevention of fragility fractures, particularly **re-fractures,** remains a significant challenge in clinical practice. Despite available therapies, **long-term treatment adherence** and **post-fracture care** are suboptimal.

Current Gaps and Challenges

- Nearly **80% of patients** with **fragility fractures** (e.g., hip or vertebral) or those on **chronic glucocorticoid therapy**:
  - Are **not accurately diagnosed**.
  - Do **not receive adequate medical intervention**.
- **Only 50%** of patients continue prescribed **osteoporosis therapy** one year after initiation.
- These gaps underscore the urgent need for **structured, multidisciplinary care models** to improve outcomes.

Proposed Integrated and Multidisciplinary Models

To address these deficits, several **evidence-based care frameworks** have emerged:

1. **Orthopaedic and Geriatric Co-Management**
   - Joint care model integrating **orthopaedic surgeons and geriatricians**.
   - Focus on comprehensive **perioperative management** and **early rehabilitation**.
   - Improves outcomes such as **mobility, length of stay**, and **readmission rates**.
2. **Fracture Units**
   - Specialized hospital units dedicated to the **care of fragility fracture patients**.
   - Facilitate standardized protocols, early intervention, and coordinated rehabilitation.
3. **Fracture Liaison Services (FLS)**
   - A **coordinated post-fracture care pathway**.
   - Aims to identify, evaluate, and treat patients with osteoporosis after a fracture.
   - Has shown success in **improving diagnosis**, **treatment initiation**, and **adherence**.

These models are **flexible and adaptable**, making them implementable across diverse **clinical settings and healthcare systems**.

The Critical Role of Nursing in Fracture Prevention

Nurses with expertise in osteoporosis and fragility fractures, such as **Bone Health Nurses** or **Nurse Case Managers**, play a pivotal role in these integrated models:

- **Care coordination** across orthopaedic teams, primary care providers, and specialists.

- **Patient education** from the point of admission:
  - Importance of **medication adherence**.
  - Strategies for **fall prevention**.
  - Lifestyle and **nutrition counselling**.
- **Family and caregiver support**, ensuring continuity of care beyond discharge.
- Monitoring for **early signs of non-compliance or recurrent risk**.

This nursing leadership is essential to ensuring the **effectiveness and sustainability** of secondary prevention initiatives.

Secondary fracture prevention requires a **systematic and team-based approach**. Implementation of integrated care models supported by **skilled nursing roles** can significantly improve:

- **Diagnosis rates**
- **Therapy initiation and adherence**
- **Functional recovery**
- **Re-fracture prevention**

A shift toward **multidisciplinary collaboration and patient-centred care** is crucial for reducing the global burden of fragility fractures.

UNDERDIAGNOSIS OF OSTEOPOROSIS IN THE ELDERLY

Osteoporosis remains significantly underdiagnosed and undertreated among the elderly, particularly in individuals over 80 years of age, despite its high prevalence and associated risks. Even when older adults present with fragility fractures, there is a notable underutilization of effective treatment options. This gap in care is especially concerning given that the elderly often represent a frail population with multiple comorbidities and an increased risk of adverse events.

Effective management of osteoporosis in this demographic necessitates treatment options that are not only efficacious but also safe and convenient. Therapies such as bisphosphonates (e.g., alendronate, risedronate, zoledronic acid), denosumab, and teriparatide have demonstrated significant reductions in both vertebral and nonvertebral fracture risks among the elderly. For instance, once-yearly intravenous zoledronic acid has been associated with a significant reduction in the risk of new clinical fractures in elderly patients. Similarly, denosumab has shown efficacy in reducing fracture risk in older adults.

Despite the availability of these effective treatments, studies indicate that a substantial proportion of elderly patients with osteoporosis do not receive appropriate therapy. This underdiagnosis and undertreatment contribute to increased morbidity and mortality in this vulnerable population. Addressing this issue requires a concerted effort to improve diagnosis rates and ensure that elderly patients receive timely and appropriate osteoporosis management.

INFLUENCE OF LIFESTYLE ON OSTEOPOROSIS RISK

Lifestyle factors significantly influence osteoporosis risk, yet awareness and preventive behaviours remain insufficient, particularly among men. A study involving men aged 36–55 revealed low levels of osteoporosis knowledge and perceived susceptibility, underscoring the need for targeted educational initiatives to address this gap.

Physical activity, especially weight-bearing exercises, plays a crucial role in enhancing bone strength. Such activities stimulate favourable geometric adaptations in bones, improving structural integrity independently of changes in bone mineral density (BMD) . While walking is a common and accessible form of exercise, its impact on increasing BMD is modest. However, it can help maintain existing bone mass and reduce the rate of bone loss. In contrast, higher-impact activities like jumping or resistance training are more effective in stimulating bone growth and improving BMD.

For postmenopausal women, combining exercise interventions with adequate nutrition, including sufficient intake of calcium and vitamin D, can mitigate the risks of osteoporosis and sarcopenia. Regular physical activity not only strengthens bones but also enhances muscle mass and balance, reducing the likelihood of falls and associated fractures.

In summary, adopting a lifestyle that incorporates weight-bearing and resistance exercises, along with proper nutrition, is essential for maintaining bone health and preventing osteoporosis. Increasing awareness, particularly among men, about the importance of these lifestyle choices is critical in reducing the incidence and impact of osteoporosis.

THE IMPACT OF CANCER-INDUCED OSTEOPOROSIS

Cancer-induced osteoporosis arises from both the direct effects of malignancies on bone and the adverse impacts of cancer therapies. Bone is a common site for metastasis, particularly in breast and prostate cancers, with approximately 70% of patients with advanced breast cancer and up to 90% with advanced prostate cancer developing bone metastases.

Bone metastases can be classified as osteolytic or osteoblastic. Osteolytic lesions result from tumour cells releasing parathyroid hormone-related peptide (PTHrP), which stimulates the production of receptor activator of nuclear factor kappa-B ligand (RANKL), leading to increased osteoclast activity and bone resorption. Conversely, osteoblastic metastases involve the proliferation and differentiation of osteoblasts, leading to abnormal bone formation.

Cancer treatments themselves can induce osteoporosis. Androgen deprivation therapy (ADT), commonly used in prostate cancer, significantly increases the risk of osteoporosis, with studies showing a 1.6-fold increase in osteoporotic fractures. Similarly, oestrogen deprivation therapies, including aromatase inhibitors used in breast cancer, accelerate bone loss by promoting osteoclast-mediated bone resorption.

Radiation therapy can also contribute to bone loss by reducing blood flow and oxygenation to bone tissue, impairing bone-forming cells, and leading to bone atrophy. These effects underscore the importance of monitoring bone health in cancer patients and implementing preventive measures, such as calcium and vitamin D supplementation, weight-bearing exercises, and pharmacologic interventions like bisphosphonates or denosumab, to mitigate the risk of osteoporosis and fractures.

THE RELATIONSHIP BETWEEN DEMENTIA AND OSTEOPOROSIS

Alzheimer's disease (AD) and osteoporosis are prevalent chronic degenerative disorders in the elderly, sharing several risk factors such as aging, reduced physical activity, vitamin D deficiency, and low body mass index. These commonalities contribute to an increased susceptibility to both conditions.

Notably, individuals with AD face a significantly higher risk of hip fractures compared to those without dementia. Studies indicate that the risk of hip fracture in patients with dementia is approximately 2.8 times higher than in non-dementia individuals, with the risk peaking within two years following a dementia diagnosis. This elevated risk is attributed to factors such as impaired balance, gait disturbances, and an increased propensity for falls, which are common in dementia patients.

Emerging research suggests that the pathophysiological mechanisms of AD may directly influence bone health. Amyloid beta (Aβ), a peptide implicated in AD, has been found to accumulate in bone tissue, where it can disrupt bone remodelling processes. Specifically, Aβ can inhibit osteoblast differentiation and promote osteoclast activity, leading to decreased bone formation and increased bone resorption, thereby contributing to osteoporosis.

Furthermore, the Wnt/β-catenin signalling pathway, crucial for both bone formation and neuronal health, is disrupted in AD. Inhibition of this pathway by Aβ accumulation not only exacerbates neurodegeneration but also impairs bone formation, highlighting a shared molecular mechanism underlying both diseases. Given the intertwined nature of AD and osteoporosis, it is imperative to adopt integrated management strategies. Early screening for bone density loss in dementia patients, coupled with interventions such as vitamin D supplementation, physical therapy to improve balance and strength, and pharmacological treatments targeting bone resorption, can mitigate fracture risks. Additionally, understanding the shared molecular pathways offers potential for developing therapeutics that concurrently address both cognitive decline and bone deterioration.

CONCLUSION

Osteoporosis is one of the most common age-associated conditions and a major cause of fracture risk. In old age, osteoporosis and osteoporotic fractures tend to occur in a particularly frail subset of the population. The treatment of osteoporosis is of particular concern in the elderly because of the substantial burden of osteoporotic fractures in terms of morbidity, mortality, and economic cost.

It is never too late to treat osteoporosis, not even in elderly patients with the most severe degree of osteoporosis and who have already sustained osteoporotic fractures. Calcium and vitamin D supplementation is an essential but not sufficient component of the management of osteoporosis in old age. Adding osteoporosis treatment appears to be safe and reduces the risk of fractures even more, at least in older individuals with documented osteoporosis and for vertebral fractures, and possibly also for hip fractures. Osteoporosis treatment may even be more effective in frail elderly patients with documented osteoporosis than in younger patients, with more fractures averted and even lower numbers to treat, ultimately leading to reduced morbidity and even mortality.

REFERENCES

1. Bowers BL, Drew AM, Verry C. Impact of pharmacist-physician collaboration on osteoporosis treatment rates. Ann Pharmacother. 2018

2. Lötters FJB, van den Bergh JP, de Vries F, et al. Current and future incidence and costs of osteoporosis-related fractures in the Netherlands: combining claims data with BMD measurements. Calcif Tissue Int. 2016

3. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2015

4. Klop C, Welsing PMJ, Elders PJM, Overbeek JA, Souverein PC, Burden AM, van Onzenoort H, Leufkens HG, Bijlsma JW, de Vries F. Long-term persistence with anti-osteoporosis drugs after fracture. Osteoporos Int. 2015

5. Netelenbos JC, Geusens PP, Ypma G, Buijs SJ. Adherence and profile of non-persistence in patients treated for osteoporosis-a large-scale, long-term retrospective study in the Netherlands. Osteoporos Int. 2017

6. Fatoye F, Smith P, Gebrye T, Yeowell G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. BMJ Open. 2019

7. Hiligsmann M, Rabenda V, Gathon HJ, et al. Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int. 2015

8. Ross S, Samuels E, Gairy K, et al. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value Heal. 2016

9. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int. 2018

10. Hiligsmann M, Salas M, Hughes DA, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. Osteoporos Int. 2018

11. Kini V, Ho PM. Interventions to improve medication adherence: a review. JAMA. 2018

12. Seng EK, Rains JA, Nicholson RA, Lipton RB. Improving medication adherence in migraine treatment. Curr Pain Headache Rep. 2015

13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2019

14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews

and meta-analyses: the PRISMA statement. PLoS Med. 2019

15. Lehane E, McCarthy G. Medication non-adherence—exploring the conceptual mire. Int J Nurs Pract. 2018

16. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2017

17. Presley B, Groot W, Pavlova M (2018) Pharmacy-led interventions to improve medication adherence among adults with diabetes: a systematic review and meta-analysis. *Res Soc Adm Pharm*:1–11. 10.1016/j.sapharm.2018

18. Morfeld J-C, Vennedey V, Müller D, Pieper D, Stock S. Patient education in osteoporosis prevention: a systematic review focusing on methodological quality of randomised controlled trials. Osteoporos Int. 2017

19. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2015

20. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2017

21. Ganda K, Schaffer A, Pearson S, Seibel MJ. Compliance and persistence to oral bisphosphonate therapy following initiation within a secondary fracture prevention program: a randomised controlled trial of specialist vs. non-specialist management. Osteoporos Int. 2015

22. Ducoulombier V, Luraschi H, Forzy G, et al. Contribution of phone follow-up to improved adherence to oral osteoporosis treatment. Am J Pharm Benefits. 2015

23. Tamechika S-Y, Sasaki K, Hayami Y, et al. Patient satisfaction and efficacy of switching from weekly bisphosphonates to monthly minodronate for treatment and prevention of glucocorticoid-induced osteoporosis in Japanese patients with systemic rheumatic diseases: a randomized, clinical trial. Arch Osteoporos. 2018

24. Cram P, Wolinsky FD, Lou Y, Edmonds SW, Hall SF, Roblin DW, Wright NC, Jones MP, Saag KG, PAADRN Investigators Patient-activation and guideline-concordant pharmacological treatment after bone density testing: the PAADRN randomized controlled trial. Osteoporos Int. 2016

25. Danila MI, Outman RC, Rahn EJ, Mudano AS, Redden DT, Li P, Allison JJ, Anderson FA, Wyman A, Greenspan SL, LaCroix A, Nieves JW, Silverman SL, Siris ES, Watts NB, Miller MJ, Curtis JR, Warriner AH, Wright NC, Saag KG. Evaluation of a multimodal, direct-to-patient educational intervention targeting barriers to osteoporosis care: a randomized clinical trial. J Bone Miner Res. 2018

26. van den Berg P, van Haard PMM, van der Veer E, et al. A dedicated fracture liaison service telephone program and use of bone turnover markers for evaluating 1-year persistence with oral bisphosphonates. Osteoporos Int. 2018

27. Bianchi ML, Duca P, Vai S, Guglielmi G, Viti R, Battista C, Scillitani A, Muscarella S, Luisetto G, Camozzi V, Nuti R, Caffarelli C, Gonnelli S, Albanese C, de Tullio V, Isaia G, D'Amelio P, Broggi F, Croci M. Improving adherence to and persistence with oral therapy of osteoporosis. Osteoporos Int. 2015

28. LeBlanc A, Wang AT, Wyatt K, Branda ME, Shah ND, van Houten H, Pencille L, Wermers R, Montori VM. Encounter decision aid vs. clinical decision support or usual care to support patient-centered treatment decisions in osteoporosis: the osteoporosis choice randomized trial II. PLoS One. 2015

29. Gonnelli S, Caffarelli C, Rossi S, di Munno O, Malavolta N, Isaia G, Muratore M, D'Avola G, Gatto S, Minisola G, Nuti R. How the knowledge of fracture risk might influence adherence to oral therapy of osteoporosis in Italy: the ADEOST study. Aging Clin Exp Res. 2016

30. Oral A, Lorenc R. Compliance, persistence, and preference outcomes of postmenopausal osteoporotic women receiving a flexible or fixed regimen of daily risedronate: a multicenter, prospective, parallel group study. Acta Orthop Traumatol Turc.