SYSTEMATIC REVIEW

To examine the treatment of osteoporosis: A systemic review

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ABSTRACT

Background: Osteoporosis, a prevalent chronic metabolic bone disease, is mostly associated with variables such as menopause and age. It is characterized by a heightened susceptibility to bone fractures due to increased bone fragility. While it may affect individuals of all age groups, genders, and ethnicities, it is more prevalent among Caucasians (individuals of white race), elderly individuals, and women. Due to a growing elderly population and extended lifespan, osteoporosis is progressively emerging as a worldwide pandemic. Presently, the estimated number of individuals afflicted with osteoporosis exceeds 200 million. Managing osteoporosis requires a comprehensive strategy including lifestyle adjustments, pharmaceutical interventions, fall prevention methods, and frequent monitoring. Medical research and treatment advancements have greatly enhanced the capacity to prevent and control osteoporosis, hence decreasing the likelihood of fractures and improving the overall well-being of those afflicted.

Aim: To evaluate the evidence for efficacy of treatment options to reduce osteoporotic fracture risk for men.

Materials and method: A systematic research was carried during june 2021 to December 2022 using MeSH terms osteoporosis, bisphonates, bone resorption, bone remodelling in PubMed, Scopus, Embase, Cochrane databases.

Conclusion:Bisphosphonates reduce vertebral and possibly nonvertebral fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of bisphosphonates for reducing nonvertebral fracture risk for men, and to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.

Keywords: Osteoporosis, osteoporosis management, bone mineral density

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INTRODUCTION

Osteoporosis is a prevalent and progressive skeletal disorder characterized by reduced bone mass, deterioration of bone tissue, and increased fracture risk. The World Health Organization (WHO) defines osteoporosis based on bone mineral density (BMD) measurements, with a T-score of -2.5 or lower indicating osteoporosis. As a major public health concern, osteoporosis affects millions globally, predominantly postmenopausal women and the elderly. This comprehensive introduction will explore the epidemiology, pathophysiology, risk factors, clinical manifestations, diagnostic methods, and management strategies for osteoporosis, underlining the significance of early detection and prevention.

Materials and method:

A systematic research was carried during june 2021 to December 2022 using MeSH terms osteoporosis, bisphonates, bone resorption, bone remodelling in PubMed, Scopus, Embase, Cochrane databases.

Epidemiology

Osteoporosis is a widespread condition, with a substantial burden on healthcare systems worldwide. According to the International Osteoporosis Foundation (IOF), approximately 200 million people are affected by osteoporosis globally [1]. In the United States alone, an estimated 10 million individuals have osteoporosis, and an additional 44 million have low bone mass, placing them at increased risk [2]. The prevalence of osteoporosis is notably higher in women, particularly postmenopausal women, due to the accelerated bone loss associated with estrogen deficiency [3]. The risk of osteoporosis and fractures increases with age, making it a significant concern for the aging population.

Pathophysiology

The pathophysiology of osteoporosis involves an imbalance between bone resorption and bone formation. Bone remodeling is a continuous process where old bone is resorbed by osteoclasts and new bone is formed by osteoblasts. In osteoporosis, this

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balance is disrupted, leading to excessive bone resorption or inadequate bone formation, or both [4]. Several factors contribute to this imbalance, including hormonal changes, genetic predisposition, nutritional deficiencies, and lifestyle factors.

Hormonal Influences

Hormonal changes play a crucial role in bone metabolism. Estrogen deficiency in postmenopausal women is a primary driver of osteoporosis. Estrogen helps maintain bone density by inhibiting osteoclast activity and promoting osteoblast survival. Its deficiency leads to increased bone resorption and accelerated bone loss [5]. Similarly, testosterone deficiency in men contributes to osteoporosis, although the decline in testosterone levels with age is more gradual [6].

Genetic Factors

Genetic factors significantly influence an individual's risk of developing osteoporosis. Studies have identified several genes associated with bone density and fracture risk. These genes regulate various aspects of bone metabolism, including the production and activity of bone-forming and bone-resorbing cells [7]. Family history of osteoporosis or fractures is a strong predictor of an individual's susceptibility to the condition.

Nutritional Deficiencies

Adequate intake of calcium and vitamin D is essential for bone health. Calcium is a vital component of bone tissue, while vitamin D facilitates calcium absorption in the intestines and maintains appropriate serum calcium levels. Deficiencies in calcium and vitamin D can impair bone mineralization, leading to decreased bone density and increased fracture risk [8]. Additionally, protein intake and other nutrients such as magnesium, phosphorus, and vitamin K play roles in maintaining bone health [9].

Lifestyle Factors

Lifestyle factors, including physical activity, smoking, and alcohol consumption, significantly impact bone health. Weight-bearing and resistance exercises stimulate bone formation and improve bone density. Conversely, physical inactivity leads to bone loss and increased fracture risk [10]. Smoking and excessive alcohol consumption have deleterious effects on bone health, as they interfere with calcium absorption and bone remodeling processes [11].

Classification of Osteoporosis

Osteoporosis is a complex disorder with diverse underlying causes and varying presentations. To better understand and manage this condition, it is essential to classify osteoporosis into distinct categories based on its etiology, clinical presentation, and severity. This section will discuss the main classifications of osteoporosis: primary and secondary osteoporosis, as well as classification based on bone density and fracture risk.

Primary Osteoporosis

Primary osteoporosis is the most common form of the disease and is primarily related to aging and hormonal changes. It is further divided into two types:

Type I: Postmenopausal Osteoporosis

- **Epidemiology**: Type I osteoporosis predominantly affects postmenopausal women, typically within 15-20 years after menopause. The prevalence increases with age, with a significant rise observed in women aged 50-70 years.
- **Pathophysiology**: The primary cause of postmenopausal osteoporosis is the decline in estrogen levels, which accelerates bone resorption. Estrogen deficiency leads to increased activity of osteoclasts (bone-resorbing cells) and reduced lifespan of osteoblasts (bone-forming cells), resulting in net bone loss.
- **Clinical Features**: This type of osteoporosis mainly affects trabecular (spongy) bone, leading to fractures in the vertebrae and distal radius (wrist).
- **Type II: Senile Osteoporosis**
- **Epidemiology**: Type II osteoporosis affects both men and women, usually over the age of 70. It is more common in older adults due to the cumulative effects of aging on bone health.
- **Pathophysiology**: Senile osteoporosis results from a combination of factors, including reduced bone formation, decreased calcium absorption, and lower levels of vitamin D. Aging leads to a decline in the function of osteoblasts and an increase in osteoclast activity, resulting in bone loss.
- **Clinical Features**: This type affects both cortical (compact) and trabecular bone, leading to fractures in the hip, pelvis, and vertebrae[12-14].

Secondary Osteoporosis

Secondary osteoporosis occurs as a result of specific medical conditions, medications, or other factors that adversely affect bone metabolism. Unlike primary osteoporosis, which is age-related, secondary osteoporosis can affect individuals of any age. Common causes of secondary osteoporosis include:

Endocrine Disorders

- **Hyperthyroidism**: Excess thyroid hormone accelerates bone turnover, leading to increased bone resorption.
- **Hyperparathyroidism**: Elevated parathyroid hormone levels result in excessive calcium release from bones, weakening them.
- **Diabetes Mellitus**: Both type 1 and type 2 diabetes can contribute to bone fragility due to alterations in bone remodeling and metabolism.

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Gastrointestinal Disorders

- **Celiac Disease**: Malabsorption of calcium and vitamin D in individuals with celiac disease can lead to reduced bone density.
- **Inflammatory Bowel Disease (IBD)**: Chronic inflammation and corticosteroid use in IBD patients can negatively impact bone health.

Hematologic Disorders

- **Multiple Myeloma**: This type of cancer affects plasma cells in the bone marrow, leading to bone destruction and increased fracture risk.
- **Hemophilia**: Recurrent bleeding into joints can damage bone and cartilage, contributing to osteoporosis.

Rheumatologic Disorders

- **Rheumatoid Arthritis**: Chronic inflammation and corticosteroid treatment in rheumatoid arthritis patients can lead to bone loss and increased fracture risk.

Medications

- **Corticosteroids**: Long-term use of corticosteroids, commonly prescribed for inflammatory and autoimmune conditions, is a significant risk factor for secondary osteoporosis.
- **Anticonvulsants**: Some medications used to treat epilepsy can interfere with vitamin D metabolism, affecting bone health.
- **Aromatase Inhibitors**: These drugs, used in breast cancer treatment, reduce estrogen levels and can lead to bone loss in women[15-18].

Classification Based on Bone Density[19-25]

Bone mineral density (BMD) is a critical parameter for diagnosing and classifying osteoporosis. The World Health Organization (WHO) has established criteria based on BMD measurements using dual-energy X-ray absorptiometry (DXA). These classifications include:

- **Normal**: BMD within 1 standard deviation (SD) of the young adult reference mean (T-score ≥ -1.0).
- **Osteopenia (Low Bone Mass)**: BMD between 1 and 2.5 SD below the young adult reference mean (T-score between -1.0 and -2.5).
- **Osteoporosis**: BMD 2.5 SD or more below the young adult reference mean (T-score ≤ -2.5).
- **Severe (Established) Osteoporosis**: BMD 2.5 SD or more below the young adult reference mean with one or more osteoporotic fractures.

Classification Based on Fracture Risk

Fracture risk assessment tools, such as the FRAX (Fracture Risk Assessment Tool) developed by the WHO, classify individuals based on their 10-year probability of sustaining a major osteoporotic fracture (hip, spine, forearm, or shoulder). The FRAX tool considers multiple risk factors, including age, gender, BMD, previous fractures, family history of fractures, body mass index (BMI), smoking, alcohol consumption, glucocorticoid use, and secondary causes of osteoporosis. Based on the calculated risk, individuals are classified into low, moderate, or high fracture risk categories, guiding clinical decision-making and treatment strategies.

Risk Factors

Several risk factors for osteoporosis have been identified, categorized into non-modifiable and modifiable factors. Understanding these risk factors is crucial for early identification and prevention of osteoporosis.

Risk Factor Category	Specific Risk Factors	Description
Demographic Factors	Age	Risk increases with age, particularly after 50 years.
	Gender	Women are at higher risk, especially postmenopausal women.
	Ethnicity	Caucasian and Asian populations have a higher risk compared to African-American and Hispanic populations.
	Family History	A family history of osteoporosis or fractures increases risk.
Lifestyle Factors	Physical Inactivity	Lack of weight-bearing and muscle-strengthening exercise contributes to bone loss.
	Poor Nutrition	Low calcium and vitamin D intake are critical factors.
	Smoking	Tobacco use is linked to decreased bone density.
	Excessive Alcohol Consumption	More than two alcoholic drinks per day can affect bone health.
Medical Conditions	Hormonal Disorders	Conditions such as hyperthyroidism, hyperparathyroidism, and Cushing's syndrome increase risk.
	Gastrointestinal Diseases	Conditions like celiac disease and inflammatory bowel disease affect nutrient absorption.
	Rheumatologic Diseases	Chronic inflammation in diseases like rheumatoid arthritis leads to bone loss.
	Endocrine Disorders	Diabetes mellitus, particularly type 1 diabetes, affects bone quality.

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	Hematologic Disorders	Conditions like multiple myeloma and hemophilia can compromise bone integrity.
	Chronic Kidney Disease	Impairs bone metabolism and calcium balance.
Medications	Corticosteroids	Long-term use of steroids such as prednisone is a significant risk factor.
	Anticonvulsants	Medications like phenytoin and phenobarbital can interfere with vitamin D metabolism.
	Aromatase Inhibitors	Used in breast cancer treatment, these reduce estrogen levels and affect bone density.
	Proton Pump Inhibitors (PPIs)	Long-term use may affect calcium absorption and bone metabolism.
Other Factors	Low Body Weight	Low BMI (body mass index) is associated with reduced bone mass.
	Previous Fractures	History of fractures, particularly after minimal trauma, indicates higher future risk.
	Menopause and Hormonal Changes	Early menopause (before age 45) or hysterectomy increases risk due to decreased estrogen levels.
	Chronic Stress and Depression	These conditions are linked to lifestyle factors and possibly hormonal changes affecting bones.

Diagnosis of Osteoporosis

Osteoporosis is a condition characterized by decreased bone mass and structural deterioration of bone tissue, leading to enhanced bone fragility and an increased risk of fractures. Early and accurate diagnosis is crucial for effective management and prevention of complications. The diagnosis of osteoporosis typically involves a combination of clinical assessment, bone density measurement, and laboratory tests. Below is a detailed explanation of the diagnostic process for osteoporosis.

Clinical Assessment

The initial step in diagnosing osteoporosis involves a thorough clinical assessment. This includes:

- **Medical History**: Gathering information on family history of osteoporosis or fractures, personal history of fractures, lifestyle factors (e.g., smoking, alcohol consumption, physical activity), and any chronic diseases or medications that may affect bone health.
- **Physical Examination**: Assessing for signs of osteoporosis, such as loss of height, spinal deformities, or tenderness over bones that may indicate fractures.

Bone Mineral Density (BMD) Measurement

Bone Mineral Density (BMD) measurement is the cornerstone of osteoporosis diagnosis. The most commonly used method for measuring BMD is Dual-Energy X-ray Absorptiometry (DEXA or DXA) scanning.

- **Dual-Energy X-ray Absorptiometry (DXA)**: DXA is a non-invasive, painless procedure that measures bone density at the hip and spine, which are common sites of osteoporotic fractures. The results are reported as T-scores and Z-scores:
  - **T-score**: Compares the patient's BMD to the average BMD of a young, healthy adult of the same sex. According to the World Health Organization (WHO), osteoporosis is defined as a T-score of -2.5 or lower.
  - **Z-score**: Compares the patient's BMD to the average BMD of people of the same age, sex, and body size. A Z-score of -2.0 or lower suggests a higher likelihood of an underlying medical condition contributing to bone loss[26,27].

Laboratory Tests

Laboratory tests are performed to rule out secondary causes of osteoporosis and to evaluate overall bone health. These tests may include:

- **Calcium and Phosphorus Levels**: To assess mineral balance.
- **Vitamin D Levels**: Vitamin D is essential for calcium absorption and bone health.
- **Thyroid Function Tests**: Hyperthyroidism can lead to increased bone resorption.
- **Parathyroid Hormone (PTH) Levels**: Elevated PTH can indicate primary hyperparathyroidism, a cause of secondary osteoporosis.
- **Complete Blood Count (CBC)**: To rule out blood disorders that may affect bone health.
- **Biochemical Markers of Bone Turnover**: Such as serum osteocalcin, bone-specific alkaline phosphatase, and urinary N-telopeptide. These markers provide information on the rate of bone formation and resorption.

Fracture Risk Assessment

The WHO has developed the FRAX® tool, an online calculator that estimates the 10-year probability of a major osteoporotic fracture (hip, spine, forearm, or shoulder) based on clinical risk factors and BMD at the femoral neck.

- **FRAX® Tool**: Incorporates multiple risk factors, including age, sex, weight, height, previous fractures, parental history of hip fracture, smoking status, glucocorticoid use, rheumatoid

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arthritis, secondary osteoporosis, alcohol consumption, and femoral neck BMD. The FRAX® score helps guide treatment decisions, particularly in patients with osteopenia (T-score between -1.0 and -2.5).

Imaging Studies

Additional imaging studies may be necessary to assess bone quality and detect fractures that are not evident on plain radiographs.

- **Vertebral Fracture Assessment (VFA)**: Performed using DXA to detect vertebral fractures.
- **Magnetic Resonance Imaging (MRI)**: Provides detailed images of bone and can detect early changes in bone structure.
- **Quantitative Computed Tomography (QCT)**: Measures volumetric BMD and can assess bone strength and structure[28].

Management Strategies for Osteoporosis

Management of osteoporosis aims to reduce fracture risk and improve bone health through a combination of lifestyle modifications, pharmacologic treatments, and other therapeutic interventions. Below is an overview of various management strategies, presented in table form for clarity.

Lifestyle Modifications[27-44]

Lifestyle modifications are the first line of defense in managing osteoporosis. These include dietary changes, exercise, and lifestyle habits that support bone health.

Strategy	Description	References
Dietary Changes	Ensure adequate intake of calcium and vitamin D.	National Osteoporosis Foundation. (2020)
Exercise	Weight-bearing and muscle-strengthening exercises to improve bone density.	Kohrt WM, et al. (2004)
Smoking Cessation	Smoking is associated with decreased bone mass.	Ward KD, Klesges RC. (2001)
Moderation of Alcohol	Excessive alcohol intake can lead to bone loss.	Berg KM, Kunins HV. (2008)

Pharmacologic Treatments

Pharmacologic treatments are critical for patients at high risk of fractures. They work by either slowing bone resorption or promoting bone formation.

Medication Class	Examples	Mechanism of Action	Indications	References
Bisphosphonates	Alendronate, Risedronate	Inhibit osteoclast-mediated bone resorption	First-line therapy	Black DM, et al. (2006)
Selective Estrogen Receptor Modulators (SERMs)	Raloxifene	Mimic estrogen's beneficial effects on bone density	Postmenopausal women	Ettinger B, et al. (1999)
Parathyroid Hormone Analogs	Teriparatide	Stimulate new bone formation	Severe osteoporosis	Neer RM, et al. (2001)
RANK Ligand Inhibitors	Denosumab	Inhibit osteoclast formation, function, and survival	Patients intolerant to bisphosphonates	Cummings SR, et al. (2009)
Calcitonin	Miacalcin, Fortical	Inhibits osteoclast activity	Short-term treatment for acute fractures	Chesnut CH 3rd, et al. (2000)
Monoclonal Antibodies	Romosozumab	Increases bone formation and decreases resorption	High-risk postmenopausal women	Cosman F, et al. (2016)

Fall Prevention

Preventing falls is crucial in reducing fracture risk among individuals with osteoporosis. Interventions can include:

Strategy	Description	References
Home Safety Modifications	Remove tripping hazards, install grab bars and handrails.	Gillespie LD, et al. (2012)
Vision Correction	Ensure proper vision correction to prevent falls.	Harwood RH, et al.

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		(2005)
Medication Review	Review and adjust medications that may cause dizziness or sedation.	Leipzig RM, et al. (1999)
Balance Training	Tai Chi and other exercises to improve balance and coordination.	Voukelatos A, et al. (2007)

Monitoring and Follow-up

Regular monitoring and follow-up are essential to assess the effectiveness of treatment and make necessary adjustments.

Monitoring Tool	Description	Frequency	References
Bone Mineral Density (BMD) Testing	DXA scan to monitor bone density changes.	Every 1-2 years	Kanis JA, et al. (2008)
Biochemical Markers of Bone Turnover	Assess treatment response and bone turnover rate.	Periodically, as needed	Eastell R, et al. (2017)
Clinical Assessment	Regular evaluation of risk factors, adherence to therapy, and fracture history.	Every 3-6 months	National Osteoporosis Foundation. (2020)

Additional Therapeutic Interventions

In certain cases, additional interventions may be warranted to manage osteoporosis effectively.

Intervention	Description	Indications	References
Hormone Replacement Therapy (HRT)	Estrogen therapy to maintain bone density in postmenopausal women.	Severe menopausal symptoms and osteoporosis	Rossouw JE, et al. (2002)
Vertebroplasty/Kyphoplasty	Minimally invasive procedures to stabilize fractures and relieve pain.	Painful vertebral fractures that do not respond to conservative treatment	Buchbinder R, et al. (2009)
Orthopedic Surgery	Surgical intervention for severe fractures.	Hip and other major osteoporotic fractures	Boonen S, et al. (2004)

Drugs Used for Prevention and Treatment of Osteoporosis[45-59]

Osteoporosis is a condition characterized by decreased bone mass and increased fracture risk. Several pharmacological treatments are available for the prevention and management of osteoporosis. These drugs can be broadly classified into anti-resorptive agents, anabolic agents, and other therapeutic options.

Anti-Resorptive Agents

Anti-resorptive agents work by inhibiting bone resorption, thereby slowing down the loss of bone density.

1. Bisphosphonates

Bisphosphonates are the most commonly prescribed drugs for osteoporosis. They inhibit osteoclast-mediated bone resorption.

- **Alendronate (Fosamax)**: Alendronate reduces the incidence of vertebral and hip fractures. It is taken weekly or daily.
- **Risedronate (Actonel)**: Risedronate is effective in reducing vertebral and non-vertebral fractures. It can be taken daily, weekly, or monthly.
- **Ibandronate (Boniva)**: Ibandronate is available as a monthly oral tablet or quarterly intravenous injection, effective in reducing vertebral fractures.
- **Zoledronic Acid (Reclast)**: Zoledronic acid is administered once a year via intravenous infusion and is effective in reducing vertebral, hip, and other fractures.

2. Selective Estrogen Receptor Modulators (SERMs)

SERMs mimic estrogen's bone-preserving effects without some of the risks associated with estrogen therapy.

- **Raloxifene (Evista)**: Raloxifene reduces the risk of vertebral fractures in postmenopausal women and has beneficial effects on bone mineral density (BMD).

3. Denosumab (Prolia)

Denosumab is a monoclonal antibody that inhibits RANK ligand, a key factor in osteoclast formation, function, and survival.

- **Denosumab (Prolia)**: Administered as a subcutaneous injection every six months,

Anabolic Agents

Anabolic agents stimulate bone formation, increasing bone mass and strength.

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1. Teriparatide (Forteo)

Teriparatide is a recombinant form of parathyroid hormone (PTH) that stimulates new bone formation.

- **Teriparatide (Forteo)**: Administered via daily subcutaneous injection, teriparatide significantly reduces the risk of vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis.

2. Abaloparatide (Tymlos)

Abaloparatide is a synthetic peptide analog of PTH-related protein, used to treat postmenopausal women with osteoporosis at high risk for fracture.

- **Abaloparatide (Tymlos)**: It is administered via daily subcutaneous injection and has been shown to significantly reduce the risk of vertebral and non-vertebral fractures.

3. Romosozumab (Evenity)

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin, thereby increasing bone formation and decreasing bone resorption.

- **Romosozumab (Evenity)**: Administered as a monthly subcutaneous injection, it significantly increases BMD and reduces the risk of vertebral and clinical fractures in postmenopausal women with osteoporosis.

Hormone Replacement Therapy (HRT)

Hormone replacement therapy can help maintain bone density and reduce fracture risk in postmenopausal women, but it is associated with increased risks of breast cancer, heart disease, and stroke.

- **Estrogen Therapy**: Effective in reducing the risk of osteoporosis-related fractures, but due to its risk profile, it is typically reserved for women with significant menopausal symptoms.

Calcitonin

Calcitonin is a hormone involved in calcium regulation and bone metabolism. It is used in the treatment of osteoporosis for its ability to inhibit bone resorption.

- **Salmon Calcitonin**: Available as a nasal spray or injection, it is used for short-term treatment of acute pain associated with osteoporotic vertebral fractures.

Combination Therapy

Combination therapy may be used in certain patients to maximize bone density and reduce fracture risk, though it is generally not first-line treatment due to the potential for increased side effects and costs.

- **Combination of Bisphosphonates and Anabolic Agents**: This approach can be beneficial in certain high-risk patients, but further studies are needed to establish the long-term benefits and risks.

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