

ADVANCES IN OSTEOPOROSIS MANAGEMENT: PATHOPHYSIOLOGY, THERAPEUTIC STRATEGIES, AND EMERGING MOLECULAR TARGETS

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ABSTRACT

Osteoporosis is a common metabolic bone disorder characterized by reduced bone mass and deterioration of bone microarchitecture, resulting in increased fracture risk. It predominantly affects postmenopausal women and the elderly and represents a major global health burden. The condition is classified into primary and secondary forms, depending on etiology. The pathogenesis of osteoporosis is closely associated with an imbalance in bone remodeling, where osteoclast mediated bone resorption exceeds osteoblast driven bone formation. Management of osteoporosis involves both non-pharmacological and pharmacological strategies. Lifestyle modifications, including regular exercise, adequate calcium and vitamin D intake, and avoidance of smoking and alcohol, play a crucial preventive role. Pharmacological treatments are broadly categorized into antiresorptive agents, such as bisphosphonates, selective estrogen receptor modulators, calcitonin, and denosumab, and anabolic agents like parathyroid hormone analogues. Although these therapies effectively reduce fracture risk, their long-term use is associated with limitations, including adverse effects and safety concerns. Recent research has focused on the development of novel therapeutic agents targeting specific molecular pathways, including sclerostin inhibition, Wnt/ β -catenin signaling, and inflammatory mediators. These emerging therapies offer promising alternatives; however, further studies are required to establish their long-term efficacy and safety.

KEYWORDS: Osteoporosis, Bone remodeling, Antiresorptive agents, Anabolic therapy, Wnt/ β -catenin pathway, Romosozumab, Bone mineral density.

1. INTRODUCTION

Osteoporosis is a common metabolic, non-communicable disorder of the skeletal system characterized by decreased bone mass and progressive deterioration of bone microarchitecture. As the structural integrity of bone declines, it becomes fragile and increasingly susceptible to fractures. The condition is often asymptomatic in its early stages and may go unnoticed until a fracture occurs, which can subsequently lead to serious complications or even death. The disease is often asymptomatic until fractures occur, commonly affecting the hip, spine, and wrist.^[1] Osteoporosis is now recognized as a major global health concern of the 21st century, impacting nearly 200 million individuals worldwide. The most critical outcome of this condition is a heightened risk of fractures, which significantly

contributes to disability and can even lead to premature mortality, particularly among older adults.^[2]

2. CLASIFICATION OF OSTEOPOROSIS

Osteoporosis is broadly classified into two main types: primary and secondary. Primary osteoporosis mainly occurs as a result of natural aging and is further categorized into postmenopausal, age-related (senile), and idiopathic forms. In contrast, secondary osteoporosis develops due to underlying diseases, medical conditions, or the use of certain medications.^[2]

2.1 Primary Osteoporosis

2.1.1 Postmenopausal Osteoporosis

Approximately 40–50% of women above the age of 60 are affected by osteoporosis.^[3] Estrogen is essential for maintaining bone health, as it promotes calcium retention

and helps suppress bone breakdown. However, during menopause, a decline in estrogen levels occurs, which stimulates osteoclast activity. This leads to increased bone resorption that surpasses the bone-forming capacity of osteoblasts, ultimately resulting in rapid loss of bone mass.^[4,5]

2.1.2 Senile Osteoporosis

Senile osteoporosis affects both males and females and is primarily linked to the aging process. It develops mainly due to a decline in bone formation, which may be partially associated with age-related loss of muscle mass. Compared to women, men generally experience a slower and more gradual reduction in bone mineral density (BMD). Hormones such as estrogen and testosterone play an important role in maintaining bone health; therefore, their decreased levels with advancing age contribute significantly to the development of this condition. In addition, reduced vitamin D synthesis and alterations in the cellular environment can impair osteoblast activity, further promoting age-related bone loss.^[2]

2.1.3 Idiopathic Osteoporosis

Idiopathic osteoporosis is an uncommon condition characterized by the occurrence of reduced bone density and fractures in young, otherwise healthy individuals, without any identifiable secondary cause. It typically begins before puberty and may persist during the pubertal years, affecting both males and females. The exact cause of this disorder remains unclear; however, it is often associated with decreased bone formation and a marked reduction in cancellous bone mass. Clinically, patients may present with recurrent fractures of long bones, persistent back pain, and in severe cases, difficulty in walking or even inability to walk.^[6,7]

2.2 Secondary Osteoporosis

Secondary osteoporosis accounts for a significant proportion of cases, affecting nearly two-thirds of men, over half of premenopausal women, and approximately one-third of postmenopausal women. It is defined by reduced bone mineral density (BMD) or an elevated risk of fractures due to causes other than normal aging or hormonal changes. Various contributing factors include lifestyle habits such as smoking, alcohol consumption, poor diet, and lack of physical activity, along with underlying medical conditions and the use of certain medications. A wide range of diseases and therapeutic agents can impair bone quality across all age groups.^[8] Among men, the most common cause of secondary osteoporosis is the use of exogenous glucocorticoids.^[9]

2.3 Other Types of Osteoporosis

During pregnancy and particularly during lactation, BMD may decrease as calcium is mobilized from the mother's skeleton to support fetal growth and milk production. These alterations are typically temporary and reversible, and most women do not experience noticeable clinical effects on bone health. However, if the body fails

to maintain proper compensatory mechanisms, pregnancy may contribute to disturbances in calcium metabolism and a reduction in bone mass. Although fractures associated with pregnancy and lactation are uncommon, they can occur, especially when additional secondary factors related to osteoporosis are present.^[2]

3 BONE REMODELING

Bone remodeling is a continuous and dynamic process involving the coordinated activities of bone formation and resorption, which maintains skeletal integrity and regulates calcium homeostasis in the bloodstream. Bone resorption is carried out by large multinucleated cells called osteoclasts, which break down bone tissue to release calcium required for various metabolic functions. Additionally, osteoclasts contribute to the reshaping of bones during growth, allowing them to attain their mature size and structure. While osteoclasts resorb bone at specific sites, osteoblasts are responsible for synthesizing new bone matrix, thereby maintaining overall skeletal architecture. During the growth phase, particularly in childhood, bone formation exceeds resorption to support development. However, after reaching physiological maturity, these two processes become balanced, ensuring bone homeostasis.^[10]

The bone remodeling cycle consists of six sequential phases: activation, resorption, reversal, formation, mineralization, and termination. The process begins with the activation phase, which involves the recognition of signals that initiate remodeling. During the resorption phase, osteoblasts respond to signals derived from osteocytes or systemic hormonal stimuli, leading to the recruitment and differentiation of osteoclast precursors at the remodeling site. This phase is relatively short-lived and is influenced by the strength and nature of the initiating signals. Following resorption, the reversal phase occurs, characterized by the removal of osteoclasts from the resorption site. Subsequently, the formation phase begins, during which osteoblasts replace osteoclasts and synthesize new bone matrix. Mineralization of this newly formed matrix then takes place, restoring bone strength. The process concludes with the termination phase, marked by the final differentiation of osteoblasts. The bone surface then remains in a resting state until a new cycle of remodeling is initiated.^[11]

3.1 Cells Involved in Bone Remodeling

Bone remodeling is a tightly regulated process involving multiple cell types, including osteoblasts (bone formation), osteocytes (maintenance of bone homeostasis), osteoclasts (bone resorption), and immune cells that modulate both formation and resorption.^[12]

Osteoblasts play a central role in bone formation by synthesizing and depositing new bone matrix. These cells originate from mesenchymal stem cells and produce extracellular matrix (ECM) components, particularly collagen, followed by mineralization with calcium and

phosphate to form a rigid bone structure. They also secrete growth factors such as transforming growth factor-beta (TGF- β) and insulin-like growth factors (IGFs), which promote bone formation.^[13] Osteoblast differentiation is primarily regulated by runt-related transcription factor 2 (Runx2).^[12] Some osteoblasts become embedded within the osteoid and differentiate into osteocytes.^[10] Osteocytes, located within the mineralized bone matrix, act as key regulators of bone remodeling. They form an extensive communication network through canaliculi, allowing them to detect mechanical and biochemical signals. These cells coordinate osteoblast and osteoclast activity in response to local and systemic stimuli. Osteocytes secrete sclerostin, which inhibits bone formation by suppressing Wnt signaling, while parathyroid hormone reduces sclerostin levels to promote bone formation. Both osteocytes and osteoblasts release osteoclast-regulating factors such as receptor activator of nuclear factor kappa-B ligand (RANKL) and colony-stimulating factor-1 (CSF-1), thereby facilitating bone remodeling.^[14]

Additionally, osteocytes contribute to calcium homeostasis and proper mineralization.^[15] In contrast, osteoclasts are responsible for bone resorption. These multinucleated cells arise from the monocyte/macrophage lineage and are typically found in resorption sites known as Howship's lacunae. Osteoclasts degrade the bone matrix by secreting enzymes such as tartrate-resistant acid phosphatase (TRAP) and cathepsin

K, releasing calcium and phosphate into circulation. This process is essential for maintaining mineral balance and removing aged or damaged bone. Osteoclast activity is regulated by factors such as RANKL and macrophage colony-stimulating factor (M-CSF), which control their differentiation and activation.^[16]

Immune cells also play a significant role in bone remodeling, particularly under inflammatory conditions. Innate immune cells, including polymorphonuclear neutrophils (PMNs) and monocytes/macrophages, along with adaptive immune cells, influence bone resorption. PMNs produce membrane-bound RANKL and inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Macrophages exhibit two main phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). M1 macrophages release cytokines like TNF- α , IL-1 β , and RANKL, promoting bone resorption, whereas M2 macrophages produce anti-inflammatory mediators that suppress osteoclastogenesis.^[17]

T cells further regulate bone metabolism through their subsets. Th1 cells produce TNF- α and IL-1, enhancing bone resorption, while Th17 cells release IL-17 and IL-1, promoting osteoclastogenesis via RANKL induction. In contrast, Th2 cells secrete anti-inflammatory cytokines such as IL-4 and IL-10, which inhibit osteoclast formation. Additionally, B cells contribute by producing IL-6, TNF- α , and RANKL, thereby supporting osteoclastogenesis (Fig. 1).^[18]

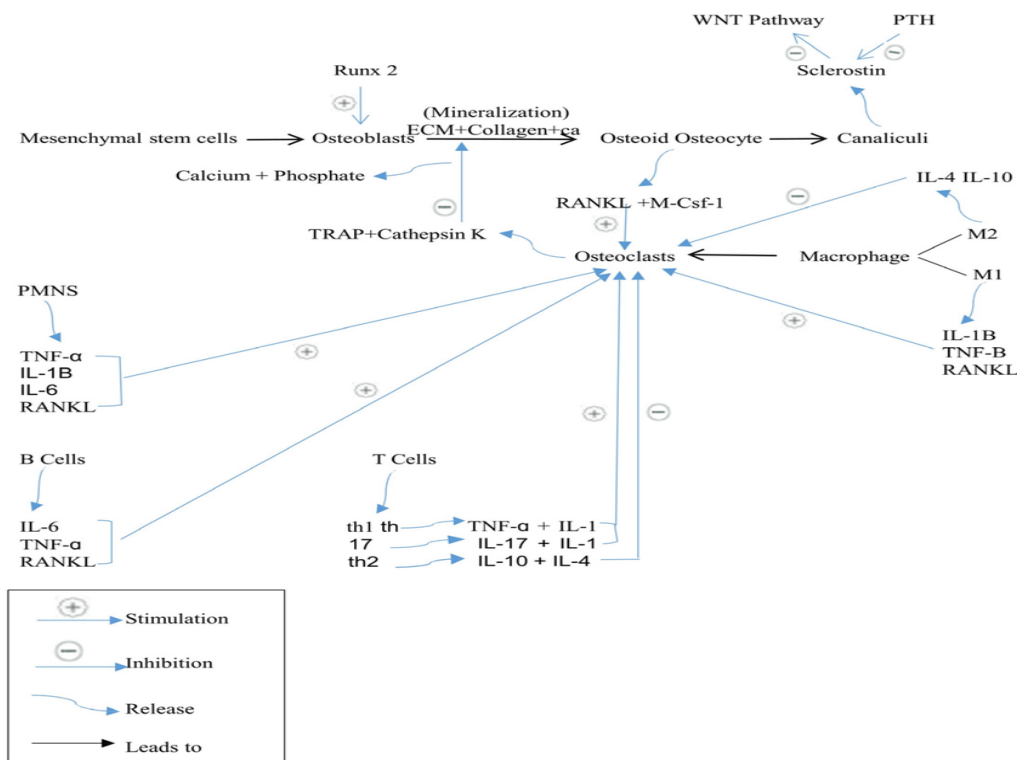


Fig. 1: The cellular mechanisms responsible for the control of bone remodeling process.^[19]

4 MANAGEMENT OF OSTEOPOROSIS

4.1 Non-Pharmacological Management of Osteoporosis

Physical activity and exercise are well-established approaches for the prevention of osteoporosis and for reducing the risk of falls and fractures. Resistance training is particularly effective, as it helps maintain skeletal muscle mass while simultaneously promoting bone formation and strength, thereby increasing BMD and lowering the risk of osteoporosis. Regular exercise, especially strength training, can delay the onset of frailty and improve overall stability and independence in older individuals. Studies have also shown that high-impact exercises are especially beneficial in increasing BMD at the femoral neck, while strength training focused on the lower limbs provides optimal outcomes. Additionally, improving core muscle strength and enhancing joint function, such as hip flexion and knee extension, can further reduce the risk of falls and musculoskeletal discomfort.

Lifestyle modifications play a crucial role in maintaining bone health and preventing osteoporosis. These include cessation of smoking, limiting alcohol consumption, ensuring adequate dietary calcium intake, and following a balanced diet rich in fruits, vegetables, and protein. Such measures contribute to improved bone metabolism and overall skeletal health.^[1]

Vitamin D is essential for calcium homeostasis and bone health, as it enhances the intestinal absorption of calcium, magnesium, and phosphate. It exists in two main forms: vitamin D₂, derived from plant sources, and vitamin D₃, synthesized in the skin and obtained from animal-based foods. Vitamin D is metabolized into its active form, calcitriol, which regulates calcium levels by acting on the intestines, kidneys, and bone, and promotes bone mineralization through activation of vitamin D receptor signaling in osteoblasts.^[20]

For optimal bone health, a daily intake of more than 800 IU of vitamin D and 700–1200 mg of calcium is generally recommended. Adequate vitamin D intake, particularly in individuals aged 50 years and above, has been shown to significantly reduce the risk of falls. However, excessive high-dose supplementation ($\geq 100,000$ IU) should be avoided due to its association with an increased risk of falls and fractures.^[21] Furthermore, calcium and vitamin D supplementation are essential in patients undergoing osteoporosis therapy, as they enhance the effectiveness of treatment and help prevent complications such as secondary hyperparathyroidism and bone metabolism disorders.^[22]

4.2 Pharmacological Management of Osteoporosis

Pharmacological management of osteoporosis is primarily aimed at reducing fracture risk by restoring the balance between bone resorption and bone formation. Drug therapy is generally recommended for individuals with low BMD, a history of fragility fractures, or those at

high risk of fractures. The available pharmacological agents are broadly classified into antiresorptive drugs, which inhibit bone resorption, and anabolic agents, which promote bone formation.

4.2.1 Antiresorptive Agents

Antiresorptive agents function by decreasing osteoclast-mediated bone resorption, thereby slowing down bone loss and improving overall bone strength. Among these, bisphosphonates are the most commonly prescribed first-line drugs for the management of osteoporosis. These agents exhibit a strong affinity for hydroxyapatite crystals in bone and preferentially accumulate at sites of active bone remodeling. They exert their action by interfering with the mevalonate pathway in osteoclasts, ultimately inducing apoptosis and reducing bone resorption.^[1]

Bisphosphonates

Commonly used bisphosphonates include alendronate, risedronate, ibandronate, and zoledronic acid. These drugs have demonstrated significant efficacy in reducing both vertebral and non-vertebral fractures and are known for their prolonged duration of action. However, their use is associated with certain limitations, including gastrointestinal irritation, particularly with oral formulations, as well as rare but serious adverse effects such as osteonecrosis of the jaw and atypical femoral fractures during long-term therapy.^[23]

Selective estrogen receptors modulators

Selective estrogen receptor modulators (SERMs) represent another class of antiresorptive agents that act by mimicking the beneficial effects of estrogen on bone tissue while antagonizing estrogenic effects in breast and uterine tissues. These agents are particularly useful in postmenopausal women, where they help maintain bone density by reducing bone resorption. Raloxifene is a commonly used SERM that has been shown to prevent bone loss and reduce the risk of vertebral fractures. Despite these benefits, SERMs are associated with certain drawbacks, including an increased risk of thromboembolic events and limited effectiveness in reducing hip fracture risk.^[24]

Calcitonin

Calcitonin is a peptide hormone that directly inhibits osteoclast activity, thereby reducing bone resorption. It is also known to provide analgesic effects in patients suffering from acute vertebral fractures. It is a useful alternative for patients with Paget's disease of bone who cannot tolerate bisphosphonates. This medication has been shown to relieve bone pain, improve neurological deficits, reduce blood flow to the affected bone, and may help improve hearing loss in Paget's disease. Unlike bisphosphonates, which may take up to three months to maximally suppress bone resorption, calcitonin acts on osteoclasts within 24–48 hours. This rapid action makes it a preferred option when urgent surgery on the affected bone is required. However, due to its relatively lower

efficacy compared to other available therapies, calcitonin is not widely used as a long-term treatment option for osteoporosis.^[25]

Monoclonal antibody

Denosumab, a monoclonal antibody, represents a more targeted therapeutic approach in osteoporosis management. It specifically binds to and inhibits the RANKL, thereby preventing the formation, activation, and survival of osteoclasts. This results in a significant reduction in bone resorption and fracture risk. Denosumab is particularly beneficial for patients who are intolerant to bisphosphonates and is administered as a subcutaneous injection every six months. However, its discontinuation may lead to rapid bone loss, and it may also cause hypocalcemia in some patients.^[26]

4.2.2 Anabolic Agents

Anabolic agents are designed to stimulate osteoblast activity and enhance new bone formation, making them especially useful in patients with severe osteoporosis or those at high risk of fractures. It is also approved for patients who develop osteoporosis due to long-term glucocorticoid therapy. Intermittent low-dose injections of teriparatide have been shown to effectively stimulate bone formation. Parathyroid hormone (PTH) analogues, such as teriparatide and abaloparatide, are widely used anabolic agents. When administered intermittently, these agents promote bone formation rather than resorption by increasing the number and activity of osteoblasts. This leads to improved bone architecture and a reduction in both vertebral and non-vertebral fracture risk. Despite their effectiveness, the use of PTH analogues is limited by their high cost and the recommended restriction on duration of therapy, which is generally up to two years.^[24]

5 LIMITATIONS OF CURRENT MEDICATIONS FOR OSTEOPOROSIS

Bisphosphonates such as alendronate, ibandronate, risedronate, and zoledronic acid, along with denosumab, are associated with several complications. The most common adverse effects are gastrointestinal, including acid reflux, pain, and esophagitis.^[23] Prolonged use of bisphosphonates may increase the risk of rare but serious conditions such as osteonecrosis of the jaw, markedly reduced bone turnover, and atypical fractures.^[27] Osteonecrosis of the jaw is reported more frequently in cancer patients receiving these therapies; however, the limited number of cases makes it difficult to confirm a clear cause–effect relationship. Further studies are needed to better understand this association and identify risk factors.

Denosumab is also associated with adverse effects such as eczema, flatulence, skin inflammation, and osteonecrosis of the jaw. Its long-term safety and efficacy remain uncertain. As it may suppress immune function, the risk of infections can increase, and some patients may develop atypical femoral fractures.

Additionally, its subcutaneous administration often requires clinical visits, which may be inconvenient for some patients.^[28]

Selective estrogen receptor modulators (SERMs) can cause hot flashes, leg cramps, and an increased risk of thromboembolism. Their long-term safety and effectiveness in osteoporosis prevention are still under investigation. Compared to bisphosphonates, SERMs may be less effective and are not suitable for patients with a history of thrombotic disorders or liver disease.^[29]

Teriparatide may cause allergic reactions in some individuals and should be avoided in patients with known hypersensitivity to the drug or its components. Its safety and efficacy are not fully established. Animal studies have indicated a potential risk of osteosarcoma, although its relevance to humans remains unclear. Therefore, teriparatide is generally reserved for patients at high fracture risk who do not respond to other treatments.^[30]

Calcitonin has several limitations, including a short half-life requiring frequent dosing, uncertain efficacy in postmenopausal osteoporosis, and the potential for antibody development with prolonged use. Due to its limited effectiveness, it is not preferred as a first-line treatment for hypercalcemia.^[25]

6 EXPECTED NEW DRUGS UNDER INVESTIGATION

Despite the availability of established pharmacological treatments, several limitations such as adverse effects, long-term safety concerns, and incomplete fracture risk reduction have driven the search for newer therapeutic options. Recent research has focused on identifying novel drugs and molecular targets that can more effectively regulate bone remodeling and improve clinical outcomes. Emerging therapies for osteoporosis are focused on targeting specific molecular pathways involved in bone remodeling. These investigational drugs offer promising alternatives to conventional therapies by providing more targeted and potentially safer treatment options. However, most of these agents are still under clinical or preclinical evaluation, and further research is required to establish their long-term efficacy and safety. The development of such novel therapies may significantly improve the future management of osteoporosis.

6.1 Romosozumab: A Dual-Action Monoclonal Antibody

Romosozumab is one of the most promising recent advancements in osteoporosis treatment. It is first FDA-approved monoclonal antibody that targets sclerostin, a protein secreted by osteocytes that inhibits bone formation.^[31] By neutralizing sclerostin, romosozumab enhances osteoblast activity and promotes bone formation. At the same time, it reduces bone resorption, thereby exhibiting a dual mechanism of action. This dual

effect distinguishes romosozumab from traditional therapies, which typically act either as antiresorptive or anabolic agents. Clinical studies have demonstrated significant improvements in bone mineral density and reduction in fracture risk. However, concerns related to cardiovascular safety have limited its widespread use, and further studies are ongoing to establish its long-term safety profile.^[1]

6.2 Cinacalcet and Calcium-Sensing Receptor Modulators

Cinacalcet is a calcium-sensing receptor (CaSR) modulator that is being explored for its potential role in osteoporosis management. It primarily acts by increasing the sensitivity of the calcium-sensing receptors in the parathyroid gland, leading to reduced PTH secretion. Since elevated PTH levels can contribute to increased bone resorption, modulation of this pathway may help in preserving bone mass. Although cinacalcet is mainly used in conditions such as hyperparathyroidism, its potential application in osteoporosis is currently under investigation. Further clinical evidence is required to determine its efficacy and safety in long-term bone health management.^[32,33]

6.3 Tiliroside: A Natural Compound with Osteoprotective Potential

Tiliroside, a naturally occurring flavonoid compound, has gained attention due to its potential bone-protective properties. It is believed to exert its effects by modulating signaling pathways involved in osteoclast differentiation and activity. Preliminary studies suggest that tiliroside may inhibit bone resorption while promoting bone formation. In addition to its effects on bone metabolism, tiliroside also exhibits anti-inflammatory and antioxidant properties, which may further contribute to its therapeutic potential in osteoporosis. However, most of the current evidence is derived from preclinical studies, and more research is needed to validate its clinical applicability.^[34]

6.4 Targeting the Wnt/ β -Catenin Signaling Pathway

The Wnt/ β -catenin signaling pathway plays a crucial role in regulating osteoblast differentiation and bone formation. Dysregulation of this pathway is strongly associated with decreased bone formation in osteoporosis. Therefore, therapeutic agents targeting this pathway are being actively investigated. Drugs that enhance Wnt signaling can stimulate osteoblast activity and promote bone formation. Sclerostin inhibitors, such as romosozumab, are an example of this approach. Future therapies may include more selective modulators of this pathway, aiming to maximize bone formation while minimizing adverse effects.^[1]

6.5 NLRP3 Inflammasome Inhibitors

Chronic inflammation is increasingly recognized as a key contributor to osteoporosis. The nucleotide-binding oligomerization domain-like-receptor family pyrin domain-containing 3 (NLRP3) inflammasome is an

important component of the inflammatory response and has been implicated in promoting osteoclast activation and bone resorption.

Inhibitors of the NLRP3 inflammasome are being investigated as potential therapeutic agents to reduce inflammation-induced bone loss. By suppressing inflammatory signaling, these agents may help restore the balance between bone formation and resorption.^[35]

6.6 P2X7 Receptor Antagonists

The purino receptor 7 (P2X7) receptor is involved in the regulation of osteoclast formation and activity. Activation of this receptor has been associated with increased bone resorption. Therefore, antagonists targeting the P2X7 receptor are being explored as a novel strategy to inhibit osteoclast-mediated bone loss. Although still in the early stages of research, targeting the P2X7 receptor offers a promising approach for the development of new antiresorptive therapies.^[36]

6.7 Sirtuin Pathway Modulators

Sirtuins are a family of proteins involved in cellular aging, metabolism, and stress responses. They have been shown to play a role in bone metabolism by influencing osteoblast differentiation and survival. Modulation of sirtuin pathways is being investigated as a potential therapeutic strategy for osteoporosis, particularly in age-related bone loss. These agents may help improve bone formation and reduce oxidative stress, thereby contributing to better bone health.^[37]

CONCLUSION

Osteoporosis remains a significant public health challenge due to its high prevalence, asymptomatic progression, and severe clinical consequences such as fractures, disability, and increased mortality. The disease arises primarily from an imbalance in bone remodeling, where increased bone resorption surpasses bone formation. A detailed understanding of its classification, underlying mechanisms, and cellular interactions is essential for effective diagnosis and management.

Current treatment strategies, including lifestyle modifications and pharmacological interventions, have substantially improved patient outcomes by reducing fracture risk and preserving bone mass. Antiresorptive and anabolic agents form the cornerstone of therapy; however, their use is often limited by adverse effects, long-term safety concerns, high cost, and patient compliance issues. These limitations highlight the need for safer, more effective, and targeted therapeutic options.

Recent advances in molecular biology and pharmacology have led to the identification of novel therapeutic targets, offering new directions for osteoporosis treatment. Emerging agents such as romosozumab and drugs targeting pathways like Wnt/ β -catenin signaling, NLRP3 inflammasome, and sirtuins represent a promising shift

toward mechanism-based therapy. Although these approaches show considerable potential, further research is necessary to validate their clinical efficacy and long-term safety.

In conclusion, the future management of osteoporosis lies in the integration of early diagnosis, preventive strategies, personalized treatment approaches, and the development of novel targeted therapies. Continued research and innovation are essential to overcome the limitations of existing treatments and to improve the quality of life of individuals affected by this debilitating condition.

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