

Review Article

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Therapeutic potential of Wnt/ β -catenin signaling pathway in osteoporosis: from molecular pathways to future clinical challenges

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Abstract

Osteoporosis represents a significant public health challenge due to its high prevalence, silent progression, and serious clinical consequences, primarily the occurrence of fragility fractures as well as the substantial economic burden it imposes on healthcare systems worldwide. Despite the availability of pharmacological treatments, current therapeutic approaches face limitations such as adverse events, suboptimal long-term efficacy, and poor patient adherence. A comprehensive understanding of the pathophysiology of osteoporosis, particularly the molecular and cellular mechanisms governing bone remodeling, is essential for the development of innovative and more effective interventions. By controlling osteoblast differentiation and bone production, the Wnt/ β -catenin signaling pathway serves as a key regulator of bone remodeling. This review brings together current understanding of the molecular processes underlying Wnt/ β -catenin signaling in bone biology, evaluates emerging therapeutic strategies that target this pathway, and highlights the clinical challenges associated with osteoporosis management.

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Osteoporosis, molecular and cellular mechanisms, Wnt/ β -catenin signaling pathway, clinical challenges

Introduction

Osteoporosis is a skeletal disease characterized by decreased bone density and deterioration of bone microarchitecture, leading to reduced bone strength and increased fragility.

Osteoporosis impacts about 32 million individuals across the European Union countries plus the United Kingdom and Switzerland (EU27+2) and leads to approximately 4.3 million new fragility fractures each year (Kanis et al., 2021). From 2017 to March 2020, hip fractures affected 2.6 million people in the United States, representing a prevalence of 2.3% (Xu et al., 2024). The lifetime risk of hip fracture in women at age 50 ranges from 7% in Romania to 25.1% in Sweden, and the average rate across the EU27+2 was 15% for women and 5.7% for men (Kanis et al., 2021).

Osteoporotic fractures are associated with significant morbidity and mortality, substantial healthcare expenditures related to treatment and rehabilitation, and a profound negative impact on patients' functional status and overall quality of life. Furthermore, the risk of subsequent fractures is significantly increased, creating a challenging cycle of declining health and functional deterioration (Iconaru et al., 2021; Merle et al., 2023; Kanis et al., 2023; Ariie et al., 2024; Lorentzon et al., 2024).

Osteoporosis represents an important challenge to public health because of its high prevalence, asymptomatic progression, and serious clinical consequences, primarily the occurrence of fragility fractures as well as the substantial economic burden it imposes on healthcare systems worldwide. Addressing this issue requires coordinated public health efforts focused on education, early detection, lifestyle modification, and effective pharmacological treatments. In clinical practice, numerous pharmacological

options are currently used to treat osteoporosis and reduce fragility fractures. However, current osteoporosis treatments face several limitations, including adverse events, suboptimal long-term efficacy, high economic burden, and challenges related to patient adherence (Gehrke et al., 2023; Yang et al., 2024; Liu et al., 2025; Mäkinen et al., 2024; Na et al., 2023).

The treatment of osteoporosis remains a significant challenge. Future directions in osteoporosis therapy are increasingly focused on overcoming the limitations of current treatments and developing more targeted, effective, and safer interventions.

Bone homeostasis relies on a tightly regulated equilibrium between osteoclast-mediated bone resorption and osteoblast-driven bone formation, involving numerous complex processes (Song et al., 2022). The intricate cellular and molecular pathways contributing to osteoporosis remain largely unclear, highlighting the need for further research (Wang et al., 2023).

A thorough understanding of the pathophysiology of osteoporosis, particularly the cellular and molecular mechanisms underlying bone remodeling and bone loss, enhances the potential for the development of innovative and more effective pharmacological interventions.

Bone remodeling is strongly regulated by the Wnt/ β -catenin signaling pathway, which promotes osteoblast development and inhibits osteoclastogenesis.

The objective of this review was to integrate and critically assess recent evidence on the molecular and cellular mechanisms underlying osteoporosis, with particular emphasis on the therapeutic potential of the Wnt/ β -catenin signaling pathway. This includes exploring its role in bone remodeling, assessing emerging pharmacological

interventions, and identifying key clinical challenges in optimizing treatment outcomes.

Material and methods

A systematic review was conducted to summarize, evaluate and synthesize previously published research related to osteoporosis. This review presents a critical and comprehensive analysis of recent advances in understanding the molecular and cellular mechanisms of osteoporosis.

A systematic literature search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies. Articles published between 2016 and 2025 were included in the review. The following key terms were used for the literature search: bone remodeling, osteoblastogenesis, osteoclastogenesis, signaling pathways related to osteoporosis, Wnt/ β -catenin signaling pathway, emerging pharmacological interventions, and future clinical challenges.

Discussion

Pathogenesis of osteoporosis

The main mechanisms underlying osteoporosis include estrogen deficiency, inflammatory processes, oxidative damage, cellular aging, and epigenetic factors, all of which promote bone resorption through enhanced osteoclastogenesis while reducing bone mineralization and formation (Zhivodernikov et al., 2023).

Bone remodeling is a lifelong, tightly regulated process that maintains a dynamic and mature skeletal architecture by balancing osteoblast-driven bone formation with osteoclast-mediated resorption (Wang et al., 2022). This continuous activity repairs skeletal microdamage, prevents the

accumulation of hyper-mineralized brittle bone, and sustains mineral homeostasis through the controlled release of calcium and phosphorus (Kenkre and Bassett, 2018).

Bone remodeling consists of sequential steps and involves contributions from three principal types of bone cells: osteoclasts, osteoblasts, and osteocytes. These cells form the active component of the basic multicellular unit and are essential for maintaining bone integrity (Marahleh et al., 2023). Osteoblasts derive from mesenchymal stem cells (MSCs) and play a key role in generating the bone matrix and enabling its mineral deposition (Siddiqui and Partridge, 2016). A certain number of osteoblasts remain fixed in the matrix as osteocytes, which are long-lived differentiated osteoblasts.

Osteocytes communicate canalicularly with bone lining cells and bone marrow cells. Through local and hormonal signals, osteocytes regulate essential physiological functions, including bone remodeling, mechanical adaptation, and mineral balance (Kitase and Prideaux, 2023). Osteocytes exhibit strong mechanosensory capabilities and are widely recognized as principal regulators of bone remodeling (Marahleh et al., 2023).

Osteoclasts are giant cells with multiple nuclei that develop from the monocyte/macrophage lineage (Ikeda and Takeshita, 2016; Udagawa et al., 2021). They play a critical role in bone remodeling through their bone-resorbing activity.

Within the basic multicellular unit, the remodeling cycle proceeds through five sequentially coordinated steps: activation, resorption, reversal, formation, and termination (Kenkre and Bassett, 2018). The coordinated actions of osteoblasts and osteoclasts in bone formation and resorption allow the integrity of the skeleton to be maintained (Jiang et al., 2023; Oton-Gonzalez et al., 2022).

Cellular and molecular mechanisms of osteoporosis

Bone remodeling is regulated by systemic and local factors, and research on rare hereditary bone diseases and animal models has elucidated the principal signaling pathways (Kenkre and Basset, 2018). The receptor activator of nuclear factor kappa-B/receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANK/RANKL/OPG) signaling pathway is crucial for bone resorption, as it regulates osteoclast differentiation and the activation of mature osteoclasts (Ono et al., 2020; Tobeiha et al., 2020). Osteoblasts secrete macrophage colony-stimulating factor (M-CSF) and RANKL, with RANKL binding to RANK on osteoclast precursors to stimulate their maturation into active osteoclasts (Oton-Gonzalez et al., 2022). OPG, also secreted by osteoblasts, acts as a soluble decoy receptor that inhibits RANKL-RANK interaction, thereby suppressing osteoclastogenesis and bone resorption (Al Anouti et al., 2019).

The Wnt/ β -catenin signaling pathway is recognized as a key regulator of osteoblastogenesis (Wang et al., 2024).

Endocrine regulation of the bone remodeling cycle involves sex hormones, parathyroid hormone, vitamin D, calcitonin, thyroid hormones, glucocorticoids, and growth hormone (Kenkre and Basset, 2018; Umur et al., 2024; Cheng et al., 2022; Yao et al., 2025; Kim et al., 2024; Rupeć et al., 2025). The coordination between bone resorption and bone formation is modulated by growth factors and immune cytokines, which have crucial role in the metabolic process (Al Anouti et al., 2019).

New insights into the cellular and molecular processes underlying bone remodeling have highlighted promising targets for pharmacological

strategies, including antiresorptive and anabolic approaches (Kenkre and Basset, 2018).

Wnt/ β -catenin signaling pathway

Osteoblasts originate from MSCs, and their differentiation into the osteoblast lineage is mediated by multiple signaling pathways (Oton-Gonzalez et al., 2022).

The Wnt/ β -catenin signaling pathway is crucial for achieving peak bone mass, as it regulates both the differentiation of osteoblasts and their bone-forming activity (Moorer and Riddle, 2018).

As a precisely regulated biochemical cascade, the Wnt/ β -catenin signaling pathway induces a specific gene expression program in the target cell (Pagella et al., 2023). The pathway is structurally divided into four segments: extracellular signals, membrane-associated components, cytoplasmic mediators, and nuclear effectors (Liu et al., 2022). It encompasses a complex network of receptors, inhibitors, activators, modulators, phosphatases, kinases, and other regulatory molecules that collectively orchestrate cellular responses essential for bone formation (Duan and Bonewald, 2016).

The Wnt/ β -catenin signaling pathway comprises key molecular components, including Wnt ligands, Frizzled (Fzd) receptors, low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors, the cytoplasmic mediator Dishevelled (Dvl), and the β -catenin destruction complex, which contains glycogen synthase kinase-3 β (GSK-3 β), axin, adenomatous polyposis coli (APC), and casein kinase 1 (CK1). These components regulate the stability and nuclear translocation of β -catenin (Figure 1).

Extracellular signals are primarily mediated by Wnt proteins, which initiate the cascade (Liu et al., 2022).

Wnt ligands initiate canonical Wnt signaling by binding to Fzd receptors and the co-receptors LRP5/6 at the plasma membrane, forming a receptor complex that triggers downstream intracellular signaling events (Oton-Gonzalez et al., 2022). Activation of this receptor complex leads to the suppression of β -catenin destruction complex activity (Song et al., 2024).

At the cytoplasmic level, key components of the Wnt/ β -catenin signaling pathway work together to regulate β -catenin stability and facilitate intracellular signal transduction (Liu et al., 2022). After stabilization, β -catenin translocates to the nucleus, where it interacts with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors to trigger the expression of targeted genes, such as matrix metalloproteinases (MMPs) and c-Myc, thereby regulating cellular proliferation and differentiation (Liu et al., 2022; Nusse and Clevers, 2017).

Runx-related transcription factor 2 (Runx2), a key downstream target of the canonical Wnt signaling pathway, regulates osteoblastogenesis and drives bone formation. The β -catenin/TCF1 transcriptional complex enhances Runx2 expression, thereby initiating a transcriptional program that drives mesenchymal stem cells toward osteoblastic differentiation (Hu et al., 2024). This process is further supported by the upregulation of downstream genes such as Sp7 transcription factor 7 (Sp7), alkaline phosphatase (ALPL), and collagen type 1 alpha 1 (COL1A1), which contribute to matrix production and mineralization (Komori, 2024; Komori, 2025). The canonical Wnt pathway, when activated, promotes an increase in bone mass (Oton-Gonzalez et al., 2022).

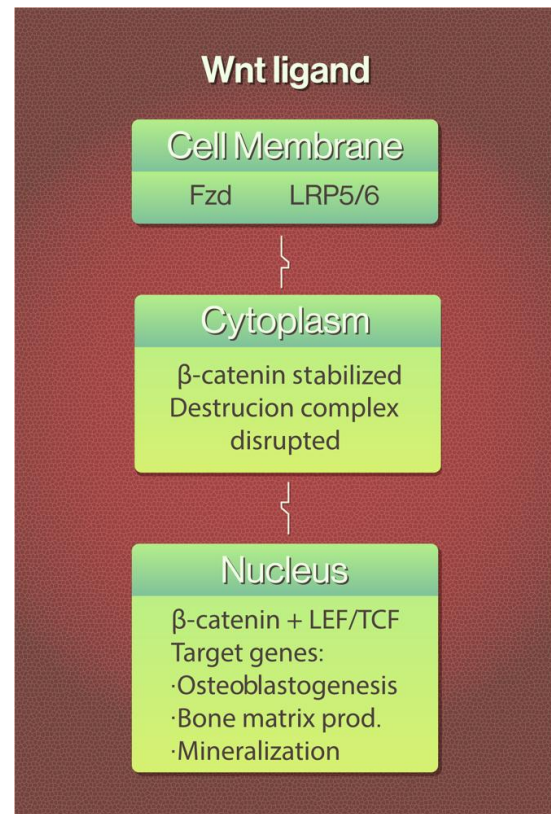


Figure 1. Activation of the Wnt/ β -catenin signaling pathway in bone cells. Binding of Wnt ligands to Fzd and LRP5/6 receptors inhibits the formation of the β -catenin destruction complex. As a result, β -catenin is stabilized, accumulates in the cytoplasm, then translocates into the nucleus and activates the transcription of genes involved in osteoblastogenesis as well as bone matrix production and mineralization.

Current pharmacological treatment of osteoporosis

Numerous pharmacological interventions are used in the management of osteoporosis, primarily categorized into antiresorptive and anabolic therapies (Figure 2). Antiresorptive drugs primarily inhibit osteoclastic bone resorption, whereas anabolic therapies primarily enhance osteoblast-mediated bone formation. Some agents exhibit a combined mechanism, simultaneously promoting bone formation and suppressing bone resorption (Gregson et al., 2025).

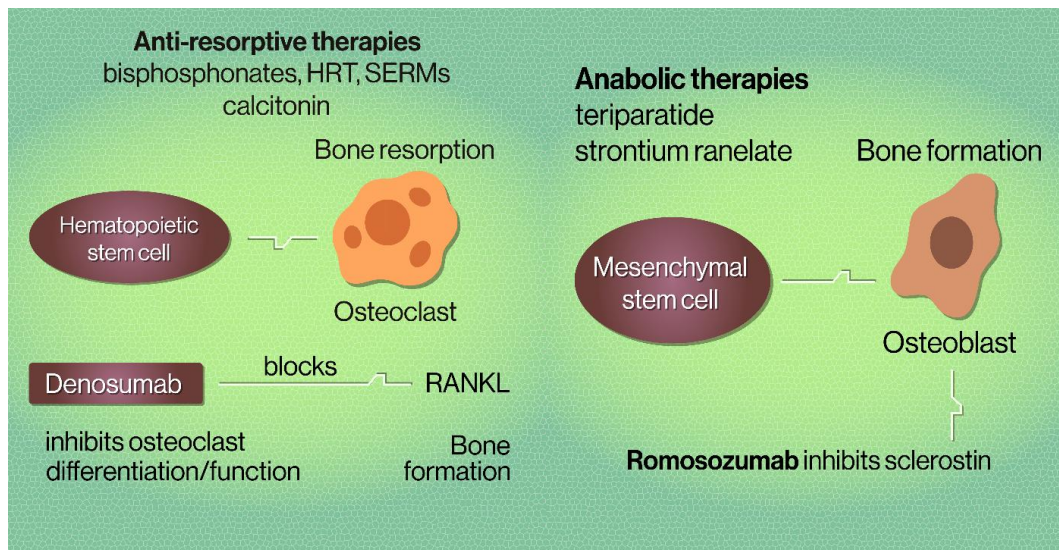


Figure 2. Therapeutic agents for osteoporosis: Mechanism of action. Anti-resorptive agents, including bisphosphonates, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and calcitonin target osteoclasts and reduce bone resorption. Anabolic agents, such as teriparatide and strontium ranelate, act on osteoblasts to stimulate bone formation. Denosumab binds RANKL, thereby inhibiting osteoclast differentiation, function, and survival. Sclerostin-targeting therapies (Romosozumab) enhance osteoblast activity and increase bone formation.

Future therapeutic strategies for osteoporosis targeting the Wnt/ β -catenin signaling pathway

Alterations in the Wnt/ β -catenin signaling pathway, whether through overactivation or reduced expression, can contribute to various diseases (Wang et al., 2024). Given its critical role in bone metabolism, the pathway has become a focus of osteoporosis research. Scientists are exploring therapies that target the Wnt signaling pathway, either by stimulating or inhibiting it, to treat osteoporosis (Gao et al., 2023). The Wnt/ β -catenin signaling pathway is essential for bone formation, as it controls the differentiation, proliferation, and function of osteoblasts. Since dysregulation of this pathway leads to impaired bone formation and an increased risk of fractures, it provides a strong rationale for exploring novel therapeutic strategies for osteoporosis that specifically target this pathway. Romosozumab, a monoclonal

antibody against sclerostin, is the first approved therapeutic agent that targets the Wnt/ β -catenin signaling pathway.

Sclerostin is a glycoprotein secreted mainly by osteocytes that acts as a bone-specific inhibitor of Wnt signaling (Marini et al., 2023). By neutralizing sclerostin, romosozumab enhances osteoblastic activity and inhibits bone resorption, resulting in significant gains in bone mineral density and reduced fracture risk (Nealy and Harris, 2021; Kobayashi et al., 2024; Kobayakawa et al., 2021). However, concerns about cardiovascular safety require careful patient selection. While romosozumab is effective for osteoporosis treatment, future strategies should focus on maintaining bone health while minimizing cardiovascular risks associated with its use, to ensure an optimal balance between efficacy and safety (Shi-Hsun et al., 2024).

Current research is concentrating on developing Wnt-targeting agents, such as small molecules,

peptides, and biologics that modulate Wnt/ β -catenin signaling with improved specificity and reduced off-target effects (Gao et al., 2023; Zhang et al., 2023; Nelson et al., 2022; Wu et al., 2025). These next-generation agents aim to address limitations of current therapies by selectively targeting key regulators of the Wnt/ β -catenin pathway to enhance bone-building effects while minimizing cardiovascular and other systemic risks. Future therapeutic approaches may involve combining of Wnt pathway modulators with traditional antiresorptive or anabolic agents to enhance synergistic drug effects, improving therapeutic efficacy in managing osteoporosis. A personalized approach could significantly improve osteoporosis management and fracture prevention. Advances in genetic profiling and biomarker discovery are driving the development of precision medicine in bone health. These emerging tools aim to enable individualized Wnt-targeted therapies tailored to each patient's risk profile, bone metabolism status, and treatment response (Ye and Liu, 2022; Yang et al., 2022; Gómez et al., 2023; Wang et al., 2020; Mäkitie and Zillikens, 2022; Verdonk et al., 2023; Furman et al., 2024; Bhattoa et al., 2025; Dincel and Jørgensen, 2023). Furthermore advancements in drug delivery and therapy systems, along with digital health interventions, have the potential to significantly improve osteoporosis management and reduce the risk of fragility fractures (Dayanandan et al., 2023; Ma et al., 2023; Gupta et al., 2022).

Conclusion

Bone loss results from an imbalance between bone resorption and formation. Among the regulatory mechanisms involved in bone metabolism, the Wnt/ β -catenin pathway has emerged as a central

regulator, promoting osteoblast differentiation and bone formation. Its pivotal role has sparked growing interest in the development of targeted therapies that either activate or inhibit this pathway to restore skeletal integrity.

Current research is focused on designing Wnt-modulating agents, such as small molecules, peptides, and biologics, with improved specificity and minimized off-target effects.

Furthermore, the integration of personalized medicine approaches and innovative drug delivery systems, alongside digital health technologies, holds promise for optimizing osteoporosis management.

Despite the availability of various pharmacological treatments, challenges such as adverse effects, limited long-term efficacy, economic burden, and patient adherence persist. Therefore, a deeper understanding of bone biology and continued innovation in therapeutic design are crucial for overcoming these limitations and improving outcomes for individuals affected by osteoporosis.

Authors' contributions

A. Kapetanović:

Conceptualization; Writing –original draft; Writing – Review & Editing.

G. Bajić:

Supervision; Writing – Review & Editing.

J. Marušić:

Supervision; Writing – Review & Editing.

DŽ. Pleho:

Supervision; Writing – Review & Editing

A. Hajrović Radović:

Supervision; Writing – Review & Editing

Conflict of interest

Authors declare no conflict of interest in relation to the publication of this article.

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