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Navigating the Antiresorptive Frontier - "The Double-Edged Bone: Molecular Mechanisms of Antiresorptive Mechanisms in Dentistry- A Narrative Review.

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ABSTRACT

Antiresorptive agents, mainly bisphosphonates and receptor activator of nuclear factor- κ B ligand (RANKL) inhibitors, are commonly prescribed to reduce skeletal complications in metabolic and cancer-related bone diseases. These drugs help maintain bone mineral density, but their broad suppression of osteoclast-driven bone remodeling poses important challenges for dental and oral-maxillofacial care.

This review synthesizes the This review brings together the main pharmacological mechanisms of major antiresorptive classes, details their primary systemic and localized adverse effects—including medication-related osteonecrosis of the jaw (MRONJ), atypical femoral fractures (AFFs), and rebound hyper-remodeling—and evaluates their specific influence on peri-implant tissues and the pathogenesis of peri-implantitis.

Introduction

Bone homeostasis relies on a balanced coupling between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Pathological states such as postmenopausal osteoporosis, Paget's disease of bone, multiple myeloma, and bone metastases disrupt this equilibrium, shifting the balance toward net skeletal degradation. Antiresorptive therapies are the cornerstone of treatment for these conditions, effectively increasing bone mineral density and reducing the risk of pathologic fractures. [1]

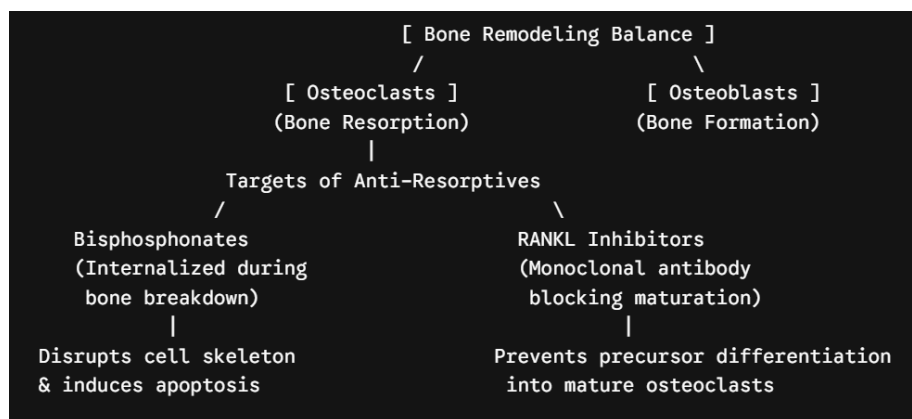
However, the widespread administration of these agents among aging populations directly overlaps with the growing demand for dental implant therapy. Because osseointegration and peri-implant marginal bone stability depend on controlled, continuous bone remodeling, the systemic administration of antiresorptive agents introduces distinct biological trade-offs. Understanding these molecular mechanisms and clinical risks is critical for managing patients presenting with peri-implant disease while on antiresorptive regimens.[1,2]

Antiresorptive therapies are widely prescribed to manage systemic skeletal disorders such as osteoporosis, Paget's disease, multiple myeloma, and bone metastases by suppressing osteoclast-mediated bone resorption. Because dental implants are increasingly placed in aging populations, the biological interplay between antiresorptive medications and peri-implant tissues—specifically in the context of peri-implantitis—has become a central topic in clinical periodontics and implantology. [3]

Anti-resorptive therapy refers to a class of medications designed to slow down or prevent the breakdown of bone (bone resorption). These drugs are primarily used to treat and manage conditions characterized by excessive bone loss or high bone turnover, such as osteoporosis, Paget's disease of bone, multiple myeloma, and bone metastases from solid tumors. By preserving existing bone matrix and slowing loss, anti-resorptive agents help maintain bone mineral density (BMD) and reduce the risk of skeletal-related events, such as pathologic fractures. [4]

Mechanisms of Action

Bone undergoes continuous remodeling through a balanced interaction between osteoclasts (cells that break down/resorb bone) and osteoblasts (cells that form new bone). Anti-resorptive therapies target osteoclasts through distinct cellular pathways, depending on the class of medication.



[Source: Rogers MJ, Crockett JC, Coxon FP, Mönkkönen J. Biochemical and molecular mechanisms of action of bisphosphonates. *Bone*. 2011;49(1):34-41. doi:10.1016/j.bone.2010.11.008.] [5]

1. Bisphosphonates

Examples: Alendronate, Risedronate, Ibandronate (oral); Zoledronic Acid, Pamidronate (intravenous).

Mechanism:

Bisphosphonates attach strongly to hydroxyapatite crystals in bone, especially where bone is being broken down. When osteoclasts start breaking down bone that contains bisphosphonates, they take up the drug into the cell. Nitrogen-containing bisphosphonates block the enzyme farnesyl pyrophosphate (FPP) synthase, which is important in the mevalonate pathway. By inhibiting the prenylation of key signaling proteins such as Ras, Rho, and Rac, bisphosphonates cause osteoclasts to lose their ruffled border, which they need to attach to and break down bone. This also leads to programmed cell death, or apoptosis. Since bisphosphonates bind directly to bone minerals, they can stay in the skeleton for many years. [1,3]

2. RANKL Inhibitors

Examples: Denosumab (Prolia, Xgeva).

Mechanism:

Targeting the RANK/RANKL pathway: Osteoblasts and stromal cells usually produce RANKL (Receptor Activator of Nuclear Factor- κ B Ligand). RANKL binds to RANK receptors on osteoclast precursors, signaling them to develop, fuse, mature, and survive.

Monoclonal antibody binding: Denosumab is a fully human monoclonal antibody that acts like the body's natural decoy receptor, osteoprotegerin (OPG). It binds tightly to RANKL and stops it from attaching to RANK on osteoclasts.

Suppression of osteoclast maturation: By blocking this interaction, denosumab prevents the formation, activity, and survival of mature osteoclasts, thereby greatly reducing bone resorption.

Reversibility: Unlike bisphosphonates, denosumab does not become part of the mineralized bone matrix. Its effect on bone resorption can be reversed when treatment stops. [1,2]

3. Selective Estrogen Receptor Modulators (SERMs)

Examples: Raloxifene, Bazedoxifene.

Mechanism:

SERMs act like estrogen in bone tissue but block it or have no effect in the uterus and breast. They attach to estrogen receptors in bone and copy the protective effects of natural estrogen. This blocks the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-alpha, which typically increase osteoclast activity. [2,3]

4. Calcitonin

Examples: Synthetic Salmon Calcitonin (nasal spray or injection).

Mechanism: Calcitonin attaches directly to receptors found on the surface of mature osteoclasts. [4,5]

When calcitonin binds, it rapidly inactivates the ruffled border of osteoclasts, causing them to detach from the bone and immediately stop bone resorption. However, calcitonin is usually seen as a weaker anti-resorptive agent than bisphosphonates or RANKL inhibitors. Anti-resorptive therapy is a group of medications that slow or prevent bone breakdown. Doctors mainly use these drugs to treat conditions with too much bone loss or high bone turnover, like osteoporosis, Paget's disease, multiple myeloma, and bone metastases from solid tumors. These medications help keep bone mineral density stable by protecting the bone matrix and slowing bone loss. This lowers the risk of complications such as pathologic fractures.

Summary Comparison of Key Classes

Drug Class	Key Target / Pathway	Effect on Osteoclasts	Retained in Bone Matrix?
Bisphosphonates	FPP synthase (Mevalonate pathway)	Disrupts cytoskeleton & causes apoptosis	Yes (long half-life in bone)
RANKL Inhibitors	RANKL ligand (blocks RANK binding)	Inhibits maturation, function, & survival	No (effects wear off when drug clears)
SERMs	Estrogen receptors in bone	Downregulates cytokine-mediated activation	No
Calcitonin	Calcitonin receptors on osteoclasts	Immediately inactivates ruffled border	No

Major drawbacks with these anti-resorptive agents

Antiresorptive agents such as bisphosphonates and denosumab help increase bone mineral density and reduce fracture risk. However, long-term suppression of osteoclast-mediated bone remodeling can lead to several important drawbacks. [2]

These drawbacks can include tissue death in specific areas and adverse effects on various organ systems. [3]

1. Medication-Related Osteonecrosis of the Jaw (MRONJ)

MRONJ is a serious oral side effect where exposed bone in the jaw does not heal for over 8 weeks in patients who have used antiresorptive therapy and have not had radiation treatment to the jaws. The jaw's ability to heal after dental work or gum disease is reduced by lower bone turnover, poor blood flow, tissue damage from bisphosphonates, and local inflammation or infection.

Risk Levels:

Low risk (less than 0.05%) is seen in patients taking low-dose oral medications for osteoporosis. High risk (1% to 5%) occurs in cancer patients who get high-dose IV bisphosphonates or frequent denosumab injections. [6]

2. Atypical Femoral Fractures (AFFs)

Oddly, keeping bone remodeling low for a long time can weaken weight-bearing long bones.

How it happens: Bone remodeling helps repair tiny cracks caused by daily stress. If osteoclasts are blocked for a long time, bones become overly hard and brittle, collecting damage that is not repaired. This can cause fractures in the thigh bone even after minor injuries.

What to look for: Patients often feel a dull, aching pain in the thigh or groin for weeks or months before a fracture. The risk goes up the longer the therapy lasts, especially after 3 to 5 years. [4,6]

3. Rebound Effect and High Calcium Levels After Stopping Denosumab

Unlike bisphosphonates, which stay in the bone for years, the effects of denosumab go away completely after stopping the drug.

How it happens: If denosumab is stopped without switching to a bisphosphonate, there is a rapid rebound in bone breakdown activity and bone turnover markers, exceeding normal levels.

Possible problems: This can cause fast and severe bone loss, very high calcium levels, and a much higher risk of several spine fractures within 6 to 12 months after stopping the drug. [2,3]

4. Gastrointestinal Problems (Oral Bisphosphonates)

Oral bisphosphonates like alendronate, risedronate, and ibandronate often irritate the upper digestive tract.

* These drugs can cause problems like esophagitis, ulcers in the esophagus, erosive gastritis, and acid reflux.

* To prevent these issues, patients must follow strict instructions: take the drug with a full glass of water first thing in the morning and stay upright for at least 30 to 60 minutes to avoid the pill sticking to the esophagus. [4,5]

5. Low Calcium and Kidney Problems

* Low calcium (hypocalcemia) happens when bone resorption is quickly reduced, so less calcium is released from bones into the blood. This is especially common with IV bisphosphonates like zoledronic acid and with denosumab, especially in patients who have low Vitamin D or serious kidney problems.

* Kidney problems: IV bisphosphonates can cause acute kidney injury or kidney failure. Zoledronic acid should not be used in patients whose estimated glomerular filtration rate (GFR) is less than 35 mL/min.[5]

6. Acute-Phase Reactions

IV bisphosphonate infusions often cause a short-term acute-phase reaction after the first dose.

* Symptoms include flu-like feelings such as fever, muscle aches, joint pain, and headaches, usually starting within 24 to 72 hours after the drug is given.

* This reaction occurs because certain immune cells in the blood rapidly release pro-inflammatory cytokines such as TNF-alpha and IL-6. [3]

Influence on Peri-Implant Dynamics and Peri-Implantitis [5-7]

Peri-implantitis is a plaque-related inflammation around dental implants. It causes soft tissue swelling and ongoing bone loss. When antiresorptive drugs are present, they change how the tissues around the implant respond.

1 Attenuated Bone Loss vs. Impaired Repair

Low-dose oral antiresorptive therapy does not usually cause bone loss around stable implants. But if biofilm builds up and peri-implantitis starts, the body cannot clear damaged bone or repair tissue as well. The normal teamwork between bone-removing and bone-building cells is disrupted during inflammation.

2 Local Drug Toxicity During Active Inflammation

In patients taking bisphosphonates, the drug stays stored in the bone around the implant. If inflammation from plaque breaks down the tissue, these drugs are released in high amounts nearby. High levels of bisphosphonates can harm nearby cells, worsen tissue damage, and slow down healing.

3 Peri-Implantitis as an MRONJ Initiator

Surgical implant placement is known to trigger MRONJ through trauma, but active peri-implantitis can also act as a local trigger due to infection. In patients on strong antiresorptive drugs, ongoing inflammation can lead to more severe bone loss, exposed bone that does not heal, and areas of jawbone death (Madeira et al., 2020).

4 Regenerative and Surgical Challenges

Surgery to treat peri-implantitis, whether removing or rebuilding tissue, is riskier for patients who have taken antiresorptive drugs. Procedures such as bone cleaning or reshaping can trigger MRONJ. Also, without working osteoclasts, the early bone breakdown needed for grafts and healing does not happen properly.

Conclusion

Antiresorptive therapies are fundamental for the management of systemic bone disorders; however, extended suppression of osteoclast activity introduces significant clinical challenges. Within dental implantology, low-dose antiresorptives do not constitute an absolute contraindication for implant maintenance. However, in patients with active peri-implantitis and antiresorptive exposure, immediate non-invasive plaque control is required to reduce the risk of progression to medication-related osteonecrosis of the jaw (MRONJ). Comprehensive risk stratification, precise soft-tissue management, and rigorous oral hygiene protocols are essential to minimize oral complications in this population.

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