Review Article

Emerging Protein and Peptide Therapeutics for Osteoporosis: Advances in Anabolic and Catabolic Treatments

Abstract

Osteoporosis is a prevalent skeletal disorder characterized by reduced bone density and increased fracture risk, primarily affecting the elderly population. The pathophysiology of osteoporosis involves an imbalance between bone resorption and bone formation, with catabolic processes (bone breakdown) counteracting anabolic processes (bone formation).Treatment strategies for osteoporosis are categorized into anabolic and catabolic approaches, each targeting different aspects of bone metabolism.Catabolic treatments focus on inhibiting bone resorption. peptide, such as Calcitonin Salmon and monoclonal antibodies like denosumab, inhibit osteoclast activity, thereby reducing bone turnover. These catabolic agents effectively stabilize bone density and reduce the incidence of fractures, especially in postmenopausal women. Anabolic treatments aim to stimulate bone formation, thereby increasing bone mass and improving bone microarchitecture. Teriparatide, a recombinant form of parathyroid hormone, and abaloparatide, a synthetic analog, and monoclonal antibody romosozumabare the primary anabolic agents. These drugs activate osteoblasts, enhancing bone formation and leading to significant improvements in bone density and reduction in fracture risk. Combining anabolic and catabolic therapies has shown promise in optimizing bone health, as it addresses both aspects of the bone remodeling process. Recent studies have shown that PEPITEM can limit bone loss and improve bone density in animal models of menopause, a common trigger for osteoporotic bone loss, and reduce bone damage in models of inflammatory bone disease, such as arthritis. Bioactive collagen peptides have shown promise as a treatment for osteoporosis by improving bone mineral density (BMD) and supporting overall bone health.

Keywords: Postmenopausal osteoporosis, Teriparatide, Denosumab, Abaloparatide, Romosozumab, Calcitonin Salmon,

1 Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass, disrupted bone architecture, and an increased susceptibility to fractures. Osteoporosis is a major noncommunicable disease and among the most common bone disease, affecting one in three women and one in five men over the age of 50 globally[1]. Globally, the prevalence of osteoporosis is estimated to be around 18.3% to 19.7% based on various studies[2]. Osteoporosis affects approximately 18% of the global population. This condition is particularly prevalent among women, with an estimated 200 million women worldwide suffering from osteoporosis.Osteoporosis is more common in women, particularly postmenopausal women, and its prevalence increases with age.The pathophysiology of osteoporosis is complex and involves an imbalance between bone resorption (the process by which osteoclasts break down bone tissue) and bone formation (mediated by osteoblasts)[3]. The pathophysiology of osteoporosis involves a multifactorial interplay of genetic, intrinsic, exogenous, and lifestyle factors that affect bone remodeling, a process crucial for maintaining bone strength and integrity[4].

Bone Remodeling Imbalance:Under normal physiological conditions, bone remodeling is a balanced process involving bone resorption by osteoclasts and bone formation by osteoblasts. In osteoporosis, this balance is disrupted, often due to increased bone resorption or decreased bone formation, resulting in net bone loss [5]. This imbalance is particularly pronounced after the third decade of life, when bone resorption begins to exceed bone formation, leading to conditions such as osteopenia and, eventually, osteoporosis[6].

Endocrine Factors:Endocrine mechanisms play a significant role in the pathophysiology of osteoporosis. Estrogen deficiency, particularly in postmenopausal women, is a major factor contributing to increased bone resorption[3]. Estrogen interacts with specific receptors on osteoblasts and osteoclasts, influencing their activity and communication, and its deficiency accelerates bone loss. Additionally, vitamin D deficiency, common in older populations, can lead to secondary hyperparathyroidism, further exacerbating bone resorption[6].

Aging and Lifestyle Factors**:** Aging is a critical factor in osteoporosis, as it leads to structural changes in bones, such as cortical thinning, increased porosity, and loss of trabecular connectivity. These changes compromise bone strength even before the onset of sex steroid deficiency. Lifestyle factors, including insufficient dietary calcium, lack of physical activity, and smoking, also contribute to the development and progression of osteoporosis [4].

Osteoclast Activity and Bone Resorption:Osteoclasts are specialized cells responsible for bone resorption. Their activity is regulated by several factors, including the RANK/RANKL/OPG (Receptor Activator of Nuclear Factor Kappa-B / RANK Ligand / Osteoprotegerin) signaling pathway. RANKL, produced by osteoblasts and osteocytes, binds to its receptor RANK on osteoclast precursors, promoting their differentiation and activation. Osteoprotegerin (OPG) acts as a decoy receptor, binding RANKL and preventing it from interacting with RANK, thereby inhibiting osteoclastogenesis[7].In osteoporosis, an increase in RANKL expression or a decrease in OPG levels can lead to enhanced osteoclast activity and increased bone resorption. Factors such as aging, estrogen deficiency (particularly in postmenopausal women), glucocorticoid use, and chronic inflammation can all contribute to this imbalance, resulting in the loss of bone density[8].

Genetic and Intrinsic Factors:Genetic predisposition plays a role in determining an individual's risk of developing osteoporosis. Genes involved in bone metabolism, such as those regulating osteoblast and osteoclast activity, can influence bone density and susceptibility to fractures. Intrinsic factors, including body weight and bone geometry, also affect bone strength and fracture risk[3].

The Wnt/β-catenin signaling pathway is a highly conserved cellular signaling mechanism that plays a crucial role in regulating various biological processes, including bone formation[9]. The Wnt/β-catenin pathway promotes bone formation by stimulating the differentiation and proliferation of osteoblasts, the cells responsible for bone synthesis[10]. It also suppresses bone resorption by inhibiting osteoclast activity, thus maintaining a balance in bone remodeling. Targeting this pathway could lead to the development of drugs that enhance bone formation and reduce fracture risk, addressing a significant unmet need in osteoporosis management[11].

In recent years, there has been growing interest in the development of protein and peptide-based therapeutics for the treatment of osteoporosis. These biologically active molecules offer the potential for more targeted and specific modulation of bone metabolism, with fewer adverse effects compared to conventional drugs. Proteins and peptides can influence key pathways involved in bone formation and resorption, such as the Wnt/β-catenin signaling pathway, the RANK/RANKL/OPG system, and the activity of osteoblasts and osteoclasts. Furthermore,

advancements in biotechnology have enabled the design and synthesis of novel peptides with enhanced stability, bioavailability, and therapeutic efficacy[11].

2 Pharmacological Treatment of Osteoporosis

Pharmacological treatments for osteoporosis are designed to either slow down bone resorption or stimulate bone formation, thereby reducing the risk of fractures and improving bone density. These treatments are broadly classified into two categories: antiresorptive (or anti-catabolic) and anabolic therapies.

Figure 1represents the bone formation (anabolic therapy) and antiresorptive (anti-catabolic) activity by the protein and peptides for the treatment of osteoporosis.

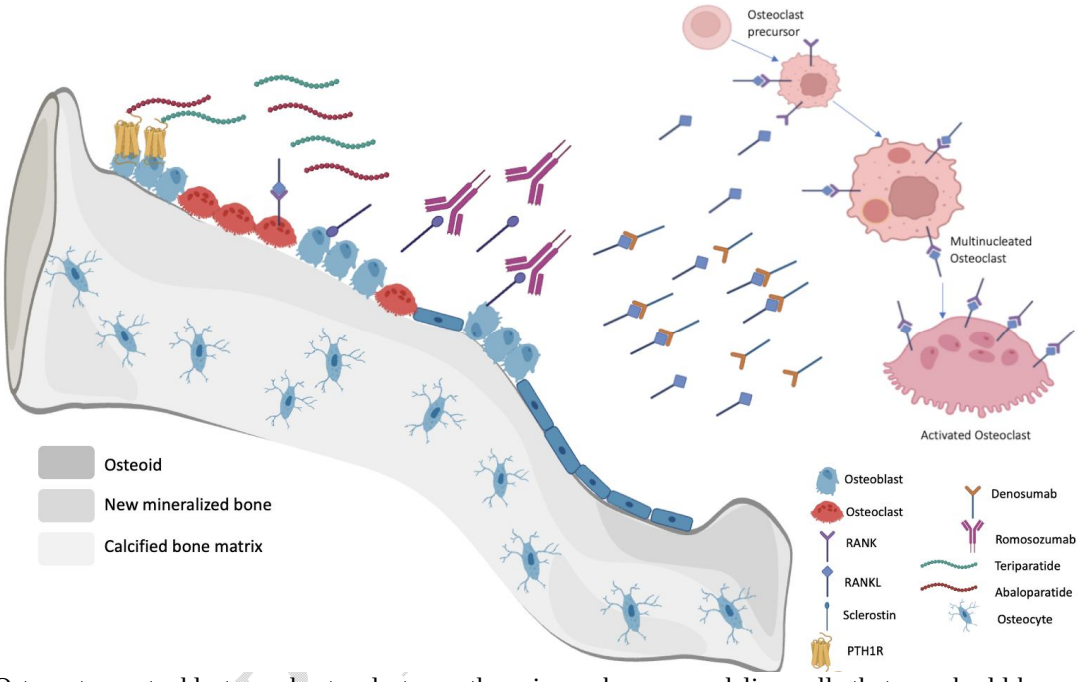

Figure 1Osteocytes, osteoblasts, and osteoclasts are the primary bone remodeling cells that resorb old bone matrix and deposit or mineralize new bone. Osteocytes and osteoblasts initiate bone remodeling and initiate the resorption process by releasing RANKL, which binds to RANK on osteoclasts and osteoclast precursors, activating osteoclasts. Denosumab binds to the cytokine RANKL, preventing it from binding to its receptor RANK. Denosumab inhibits the maturation of osteoclast precursors and promotes the apoptosis of mature, multinucleated osteoclasts by binding with cytokine RANKL. Teriparatide, a recombinant fragment of parathyroid hormone, and Abaloparatide, a PTH1 receptor agonist, promote bone formation by increasing osteoblast activity and, to a lesser extent, inhibiting osteoclast activity. Sclerostatin is a protein secreted by osteoclasts that inhibits osteoblast proliferation and function, resulting in reduced bone formation.Romosozumab is a humanized form of monoclonal antibody (IgG2) that binds to and inhibits sclerostin, promoting bone formation (Figure created from Biorender.com).

2.1 Anticatabolic or Antiresorptive drugs

2.1.1 Denosumab

Denosumab is a monoclonal antibody (mAb) developed by Amgen, marketed under the brand names Prolia and Xgeva. **Denosumab** is a RANKL (Receptor activator of nuclear factor kappa-B ligand) inhibitor, a bone anti-resorptive drug, treats osteoporosis and various bone-related disorders patients at high risk for bone fractures[12]. It is the first and only RANKL inhibitor approved for the prevention of osteoclast-mediated bone loss. Chemically, it consists of two

heavy and two light chains, with each light chain containing 215 amino acids and each heavy chain containing 448 amino acids and four intramolecular disulfides[13]. Denosumab was licensed by the FDA in June 2010 under the brand name Prolia for use in postmenopausal women at risk of osteoporosis, and as Xgeva in November 2010 to prevent skeletal-related events in patients with solid tumors that have spread to the bone. It is the first RANKL inhibitor to receive FDA approval. In the European Union, denosumab received approval for medical use as Prolia in May 2010, then as Xgeva in July 2011.

Further indication approval was granted in September 2011 to increase bone density in men at elevated risk of fracture receiving treatment with androgen deprivation for non-metastatic prostate cancer, in Sep 2012 for men with osteoporosis at extreme risk of fracture, and in Sep2011 for women at excessive risk of fracture obtaining adjuvant aromatase inhibitor therapy for breast cancer[14].Denosumab under the brand name Prolia is indicated as a treatment for osteoporosis in menopausal women or men and Glucocorticoid-induced osteoporosis in men and women at elevated risk for fracture. It is also used to increase bone density in men at high risk of fractures receiving androgen deprivation therapy for nonmetastatic prostate cancer and women at substantial risk of fractures receiving adjuvant aromatase inhibitor therapy for breast cancer [15][16]. Denosumab under the brand name Xgeva is indicated to prevent skeletal related complications in patients who have multiple myeloma, bone metastases from solid tumors, and to treat tumors with giant cells of bone in adults and skeletally mature teenagers, as well as hypercalcemia of malignancy refractory to bisphosphonate therapy [16].

Denosumab is a completely human monoclonal antibody that acts as an antiresorptive agent by targeting and inhibiting the activity of the receptor activator of nuclear factor kappa-B ligand (RANKL)[17]. RANKL is a cytokine essential for the formation, function, and survival of osteoclasts, which are cells accountable for bone resorption.By binding to RANKL, denosumab prevents it from interacting with its receptor, RANK, on the surface of osteoclasts and their precursors. This inhibition leads to a reduction in osteoclast formation and activity, resulting in reduced bone resorption and turnover [18][19].

2.1.1.1 Pharmacokinetics

Denosumab is not administered daily. Instead, the recommended dosing schedule varies depending on the specific condition being treated.

Osteoporosis (Prolia): The recommended dose is 60 mg administered as a single SC (subcutaneous) injection once every 6 months. Patients should also receive daily supplements of calcium (1000 mg) and vitamin D (at least 400 IU) to prevent hypocalcemia [20].

Giant Cell Tumor of Bone, Osteolytic Bone Metastases, and Hypercalcemia of Malignancy (Xgeva): The dosing regimen involves an initial dose of 120 mg subcutaneously on days 1, 8, and 15, followed with a maintenance dose of 120 mg every four weeks. As with Prolia, calcium and vitamin D supplementation is recommended to prevent hypocalcemia [20].

The ADME (Absorption, Distribution, Metabolism, and Excretion) profile of denosumab is characterized by the following:

Absorption: Denosumab is administered via subcutaneous injection, with a bioavailability of approximately 61%. After administration, serum concentrations of denosumab can be detected within one hour, and peak serum concentrations are typically reached between 5 to 21 days post-injection [12].

Distribution: Denosumab's pharmacokinetics is explained by a two-compartment model that includes first-order absorption and parallel linear and nonlinear elimination. It does not

incorporate into bone, which distinguishes it from some other treatments like bisphosphonates [21].

Metabolism: As a monoclonal antibody, denosumab is metabolized through proteolysis, involving the breakdown into smaller peptides and amino acids. This process is consistent with the metabolism of other protein-based therapies and does not involve cytochrome P450 enzymes[18][21][22][23].

Excretion: Denosumab is primarily eliminated through the reticuloendothelial system, with minimal renal excretion. The elimination half-life is approximately 32 days, while the terminal half-life ranges between 5 and 10 days. Denosumab can remain detectable in serum for up to nine months or more after administration [18][21][22][23].

2.1.1.2 Adverse effects

Denosumab, a monoclonal antibody used to treat osteoporosis and other bone-related conditions, is associated with several adverse effects. Common and notable side effects include,

Hypocalcemia: Denosumab can cause low calcium levels in the blood, which may lead to muscle spasms, cramps, or tingling sensations. This is particularly a concern in patients with pre-existing hypocalcemia or those on dialysis [22].

Infections: There is an increased risk of infections, including upper respiratory tract infections, urinary tract infections, and skin infections like cellulitis [22].

Musculoskeletal Pain: Patients may experience back pain, joint pain, and limb pain. Muscle and bone pain are also reported [22].

Osteonecrosis of the Jaw (ONJ): Although rare, ONJ is a serious condition associated with denosumab, especially in patients undergoing invasive dental procedures [22].

Gastrointestinal Issues: Common gastrointestinal side effects include nausea, vomiting, diarrhea, constipation, and decreased appetite [22].

Dermatologic Reactions: Skin reactions such as rashes, eczema, and dermatitis can occur.

2.1.1.3 Recommended monitoring parameters for patients on denosumab

Calcium Levels: Regular monitoring of serum calcium levels is crucial, especially in patients predisposed to hypocalcemia, such as those with severe renal damage or on dialysis. Monitoring should occur before the first injection, 1-2 weeks after administration, and periodically thereafter, as hypocalcemia can occur at any time during treatment.

Renal Function: Baseline renal function should be assessed, particularly patients with advanced chronic kidney disease (CKD), as they are at higher risk for hypocalcemia.

Vitamin D Levels: Ensure adequate levels of 25-hydroxyvitamin D before starting treatment and continue supplement with calcium and vitamin D to support bone health and prevent hypocalcemia [22].

Bone Profile: Prior to the second and each subsequent injection, check the bone profile, including albumin-adjusted serum calcium levels and electrolytes (U&Es), to ensure stability and prevent complications.

2.1.1.4 Combination therapy

Combination therapy involving denosumab has been explored to enhance the management of osteoporosis, particularly in postmenopausal women. The combination of denosumab with other osteoporosis treatments, such as teriparatide, has shown promising results in increasing bone mineral density (BMD) more effectively than monotherapy [23].

Studies have demonstrated that combining denosumab with high-dose teriparatide significantly increases BMD at the spine and hip compared to either treatment alone. This combination therapy optimizes the balance between bone formation and resorption, leading to greater

improvements in bone density and strength. The DATA-HD trial specifically highlighted that high-dose teriparatide (40 µg) combined with denosumab resulted in larger increases in BMD than standard-dose teriparatide (20 µg) combined with denosumab [23][24].

2.1.1.5 Denosumab, bisphosphonates, Anabolic drugs: similarities and differences

Denosumab is distinct from other antiresorptive agents like bisphosphonates, which work by binding to bone mineral and inducing osteoclast apoptosis. The mechanism of denosumab allows for a different onset and reversibility of treatment effects compared to bisphosphonates.

Since resorption and bone production are coupled inside the BMU (basic multicellular units), denosumab and the bisphosphonates primarily aimat osteoclasts, with predominantly indirect effects on osteoblasts.

Denosumab, like the other first-line medications, does not get ingrained in bone tissue way bisphosphonates do. Rather, denosumab prevents the development of osteoclasts via binding to RANKL in the extracellular fluid and circulation [18].

Additionally, anabolic treatments for osteoporosis, such as teriparatide, work by encouraging bone formation rather than inhibiting resorption. These treatments activate osteoblasts, the cells accountable for bone formation, and are used in a different subset of patients compared to antiresorptive therapies like denosumab and bisphosphonates.

2.1.2 Calcitonin Salmon

Salmon calcitonin, also known as calcitonin, is a derivative of human calcitonin used to treat postmenopausal osteoporosis, Paget disease of the bone, and hypercalcemia[25]. Calcitonin

Calcitonin salmon is a synthetic peptide used primarily for the treatment of postmenopausal osteoporosis in women who are at least five years beyond menopause[25].

Calcitonin salmon was first approved by the U.S. Food and Drug Administration (FDA) in 1975 for the treatment of postmenopausal osteoporosis in women more than five years post-menopause. This approval was for the nasal spray formulation, which became a significant therapeutic option due to its non-invasive administration method. The injectable form of calcitonin salmon, marketed under the brand name Miacalcin, was approved later. The injectable version was initially approved in 1986 for a concentration of 100 IU/mL and later for 200 IU/mL in 1991[26][27].

Calcitonin is a peptide hormone made up of 32 amino acids and is primarily secreted by the human thyroid gland's parafollicular cells (C cells).The hormone exists in several forms, including salmon calcitonin, human calcitonin, and a synthetic analog.Extensive research has been conducted on salmon calcitonin, revealing that it is more potent than the human variant, making it the preferred option in clinical applications.

Calcitonin-Salmon consists of 32-amino acid and is an alpha-helical polypeptide that contrasts significantly from human calcitonin, particularly in amino acids 10–27. These amino acid sequence variations account for the increased potency of salmon-derived calcitonin. Calcitonin functions through a G protein-coupled receptor (GPCR) known as the calcitonin receptor, which primarily transmits signals via the cAMP and PLC/IP3 pathways [28][29][30][31].The drug's clinical significance stems from its ability to inhibit osteoclast activity while increasing calcium excretion in the kidneys. These mechanisms slow bone matrix resorption and lower serum calcium levels. For these reasons, calcitonin is useful in treating the aforementioned conditions[32]

2.1.2.1 Pharmacokinetics

Daily administration of 100 IU of the medication via SQ or IM is recommended. The nasal spray method necessitates alternating nostrils daily and using 200 units per actuation.

Absorption:Calcitonin is available in a variety of formulations, including nasal spray, subcutaneous, and intramuscular injection. The bioavailability of calcitonin varies with the route of administration. Intranasal administration causes gradual absorption, with peak plasma concentrations reached within 15 to 40 minutes and a 3% bioavailability. SQ and IM injections produce peak plasma concentrations in 15 to 30 minutes, with a bioavailability of approximately 66%.

Distribution: Calcitonin disperses throughout the body after it is absorbed. The drug's half-life is relatively short, ranging from minutes to hours. Calcitonin readily binds to plasma proteins, particularly albumin, at a rate of about 30% to 40%. The drug distributes throughout the body, with the highest concentrations found in the kidneys, bones, and central nervous system. Calcitonin's volume of distribution ranges from 0.15 to 0.3 L/kg.

Metabolism:Calcitonin's primary metabolic processes involve proteolytic enzyme breakdown, which occurs primarily in the kidneys and other tissues.

Excretion: The primary route of elimination is through the urine. Calcitonin salmon enhances the elimination of calcium,filtered phosphate and sodium by reducing their tubular reabsorption in the kidneys

2.1.2.2 Adverse effects

Nasal Spray Side Effects

Common: Runny nose, nasal irritation, nosebleeds, sinus pain, and nasal dryness or crusting are frequently reported. Patients may also experience headaches, dizziness, back pain, and joint pain.

Serious: Nasal sores, muscle cramps, numbness or tingling in the arms or legs, and severe allergic reactions, such asitching, rash, swelling (especially of the face, tongue, or throat), severe dizziness, and breathing difficulty although rare and require immediate medical attention[32].

Injectable Form Side Effects

Common: Nausea, vomiting, abdominal pain, diarrhea, and flushing are common with injectable forms[32].

Serious: Hypersensitivity reactions, including bronchospasm, tongue swelling, anaphylactic shock, and maculopapular rashes, can occur, especially in patients allergic to fish products. Localized reactions at the injection site, such as inflammation and pruritus, may also occur[32].

Hypersensitivity: Patients with allergies to fish products may be at increased risk of hypersensitivity reactions when using salmon calcitonin[25].

Monitoring: Regular examination of the nasal mucosa is recommended for those using the nasal spray, especially if nasal symptoms develop[28].

2.2 Anabolic therapies

Anabolic treatments for osteoporosis emphasis on rousing bone formation, thereby increasing bone mineral density (BMD) and reducing the risk of fractures. These treatments are particularly beneficial for patients with severe osteoporosis or those who have not responded well to antiresorptive therapies. There are currently 3 approved anabolic therapies on the market. The PTH analogue- teriparatide, the parathyroid hormone related peptide (PTHrP) analogue- abaloparatide and the sclerostin inhibitor monoclonal antibody-romosozumab.

2.2.1 Teriparatide

Teriparatide was innovated by Eli Lilly and Company. The drug was first approved in the United States in November 2002 under the brand name Forteo. Eli Lilly developed teriparatide as the first approved anabolic therapy for osteoporosis, representing a new approach compared to traditional anti-resorptive medications. As the innovator product, Forteo by Eli Lilly was the original brand name teriparatide available on the market before generic versions were introduced[33][34].

Teriparatide is a recombinant form of parathyroid hormone (PTH) used to treat osteoporosis [35]. It consists of the first 34 amino acids of the human parathyroid hormone, which is the bioactive portion responsible for its effects on bone metabolism. Treatment with the 34 amino acid PTH analogue teriparatide (rhPTH [1-34]) has been shown to increase bone mineral density scores as assessed by DEXA scan in patients with osteoporosis, and long-term therapy has been associated with a lower rate of bone fractures[36].

Teriparatide binds to the N-terminal moiety of parathyroid hormone type 1 receptors (PTH1R), which are G-protein coupled receptors expressed on osteoblasts, osteocytes, and renal tubular cells[37]. Upon binding, teriparatide activates downstream signaling pathways, primarily the protein kinase A (PKA) and protein kinase C (PKC) dependent pathways in osteoblasts[38][39]. Teriparatide promotes the differentiation and activation of osteoblasts, the cells responsible for bone formation[40]. It upregulates the expression of pro-osteoblastogenic growth factors such as insulin-like growth factor 1 (IGF1) and fibroblast growth factor 2 (FGF2). The intermittent exposure preferentially stimulates osteoblast activity over osteoclast activity, promoting new bone formation and increasing bone mineral density (BMD). This anabolic effect is beneficial for treating osteoporosis, as it enhances bone strength and reduces fracture risk [41].

Teriparatide downregulates the synthesis of sclerostin, a protein that inhibits bone formation. Sclerostin is an inhibitor of the Wnt/β-catenin signaling pathway, which is crucial for bone formation. By downregulating sclerostin, teriparatide removes this inhibition, allowing for increased osteoblast activity and bone formation [40][37].

2.2.1.1 Pharmacokinetics

20 micrograms (mcg) administered subcutaneously once daily. The injection should be given into the thigh or abdominal wall.

The pharmacokinetic profile shows rapid absorption, a short half-life of about 1 hour, and quick elimination. The total duration of exposure is approximately 4 hours after each dose. This profile supports the once-daily subcutaneous dosing regimen used for osteoporosis treatment.

Absorption: Teriparatide is rapidly absorbed after subcutaneous injection, reaching maximum concentration (Cmax) within 30 minutes. The absolute bioavailability is approximately 95% following subcutaneous administration [41].

Distribution: The volume of distribution is approximately 0.12 L/kg following intravenous injection.

The apparent volume of distribution (V/F) following subcutaneous administration is about 7.8 L. Teriparatide is not likely to accumulate in bone or other tissues.

Metabolism: No specific metabolism studies have been performed with teriparatide. It is believed to be metabolized by non-specific enzymatic mechanisms in the liver. Peripheral metabolism of parathyroid hormone is thought to occur via non-specific enzymatic processes.

Excretion: The elimination half-life of teriparatide is approximately 1 hour following subcutaneous administration. Systemic clearance is about 62 L/hour in women and 94 L/hour in men. The high clearance rate exceeds normal liver plasma flow, suggesting both hepatic and

extrahepatic mechanisms of clearance. It is believed to be excreted via the kidneys, though specific excretion studies have not been performed[42].

2.2.1.2 Adverse effect

Teriparatide is a well-tolerated drug,patients reported short-term side effects such as nausea, headaches, dizziness, and orthostatic hypotension. Alterations in calcium metabolism are common, with hypercalcemia and hypercalciuria being the two most common complications.Hypercalcemia is most commonly mild and transient, and rarely (3% of patients taking 20 mcg/d) does it become persistent and require dose reduction or therapy discontinuation.Teriparatide increased renal calcium excretion from baseline, but no significant hypercalcemia or renal sequelae such as nephrolithiasis or nephrosclerosis were reported. Increased serum uric acid levels have been observed. A 15-year post-marketing surveillance study found that teriparatide did not increase the risk of osteosarcoma. Risk factors identified were exposure to radiation and Paget disease of bone[36].

The most common side effects tend to be mild and related to the injection itself or transient effects on calcium metabolism. However, patients should be monitored for more serious effects, particularly signs of osteosarcoma, given the theoretical risk based on animal studies. The benefits of treatment are generally considered to outweigh the risks for appropriate patients at high fracture risk[33].

Contraindications: Teriparatide is contraindicated in patients with hypersensitivity to the drug or its components, and in those with conditions that increase the risk of osteosarcoma, such as Paget's disease, unexplained elevations of alkaline phosphatase, or a history of skeletal radiation therapy.

Precautions: Caution is advised in patients with active or recent urolithiasis, hypercalcemia, or other metabolic bone diseases[33].

A 2022 review focused on the history and science behind the potential osteosarcoma risk associated with teriparatide. Despite initial concerns based on rodent studies, no cases of osteosarcoma were observed in clinical trials or postmarketing surveillance studies in humans. Consequently, the FDA removed the boxed warning for osteosarcoma in 2020, allowing for more flexible use of teriparatide in clinical practice[43].

2.2.1.3 Case Study in Lung Transplant Recipients

A recent case study published in 2024 explored the use of teriparatide in lung transplant (LTx) recipients with severe osteoporosis. The study involved three patients who were treated with teriparatide for 18 months, followed by consolidation treatment with zoledronate. The patients showed significant improvements in bone mineral density (BMD) and experienced no new fractures during the teriparatide treatment period. However, one patient sustained fractures after transitioning to zoledronate. This study highlights the potential benefits of teriparatide in improving BMD and reducing fracture risk in LTx recipients, although long-term follow-up is necessary to fully understand its efficacy and safety in this specific population [44].

A comprehensive review published in 2021 examined the real-world experience with teriparatide in treating osteoporosis across different patient groups, including postmenopausal women. The review found that extensive real-world data confirms the fracture reduction and bone mineral density (BMD) benefits of teriparatide seen in clinical trials for postmenopausal osteoporosis. This real-world evidence and long-term follow-up data support the efficacy of teriparatide in reducing fracture risk and improving bone density in postmenopausal women with osteoporosis, with benefits persisting after treatment discontinuation. The review also noted that extensive

surveillance has not identified any safety signals related to osteosarcoma risk, which was an initial concern based on preclinical studies [45].

2.2.1.4 Combination treatment of teriparatide with other drugs

Combining teriparatide with antiresorptive agents, especially denosumab, appears to offer greater improvements in BMD compared to using these medications alone in treating osteoporosis. Specifically, the combination improved lumbar spine BMD by 3.57% and hip BMD by 2.0% more than denosumab alone, and by 2.28% and 4.10% respectively compared to teriparatide alone [46][47].A randomized trial found that combining teriparatide with a single infusion of zoledronic acid increased spine BMD more rapidly than either drug alone. At 1-year, total hip BMD increased by 2.3% with the combination, compared to 1.1% with teriparatide alone and 2.2% with zoledronic acid alone [48]. Most patients starting teriparatide have previously received antiresorptive drugs. Studies show that switching from bisphosphonates to teriparatide can be effective, with the response potentially influenced by the prior bisphosphonate used [48][49].

2.2.2 Abaloparatide

Abaloparatide is an agonist at the parathyroid hormone type 1 (PTH1) receptor and the N-terminal analog of parathyroid hormone-related protein (PTHrP)[50]. It is a synthetic peptide of 34 amino acids that is 41% similar to human PTHrP 1-34 and human parathyroid hormone 1-34. The receptor-activating domain and the first 21 amino acids are shared by PTHrP and Abaloparatide. On April 28, 2017, the FDA initially approved it for the treatment of osteoporosis in postmenopausal women. It is also used to help males with osteoporosis increase their bone density [51]. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) proposed in October 2022 that Abaloparatide be given marketing authorization in Europe. The medication was fully authorized by the European Commission on December 19, 2022 [52]. Abaloparatide is a PTHrP analog that is identical to PTHrP at amino acid residues 1–21 but has some changes made between amino acids 22–34 (which are 38% identical to PTHrP) in order to increase the stability of the molecule [53].

Abaloparatide acts as an agonist at the PTH1R, stimulating the Gs-protein-mediated cyclic adenosine monophosphate (cAMP) pathway. This activation leads to the stimulation of phospholipase C (PLC) and protein kinase A (PKA), resulting in increased osteoblast activity and bone formation [54]. Abaloparatide has a greater affinity for the RG conformation of PTH1R compared to the R0 conformation. This selective binding to the RG conformation induces a rapid and transient increase in cAMP signaling, which promotes anabolic effects on bone while minimizing osteoclast-mediated bone resorption [55].

2.2.2.1 Pharmacokinetics

The recommended dosage is 80 µg administered subcutaneously once daily to the periumbilical region of the abdomen [56].

Absorption: Absolute bioavailability of Abaloparatide is 36% following administration of 80 mcg dose in healthy women. Tmax (time to peak concentration) is 0.51 hours. Cmax (peak concentration) is Mean 812 pg/mL after 7 days of 80 mcg dosing in postmenopausal women with osteoporosis[54].

Distribution: Abaloparatide has an approximate volume of distribution of 50 L, with plasma protein binding estimated at 70%.

Metabolism: Abaloparatide peptide fragments are primarily eliminated through the kidneys following nonspecific proteolytic degradation.
Elimination: The mean half-life of Abaloparatide is approximately 1hour. Abaloparatide is primarily eliminated from the body via the kidneys. Women with mild, moderate, or severe renal impairment do not need to adjust their dosage. However, close monitoring for adverse reactions is required for women with severe impairment[54][56]
The pharmacokinetics appear to be linear, with dose-proportional increases in exposure observed across the therapeutic dose range. This ADME profile indicates that Abaloparatide is rapidly absorbed after subcutaneous injection, has moderate protein binding, undergoes non-specific proteolytic degradation, and is primarily eliminated through the kidneys with a short half-life [50].

2.2.2.2 Adverse Effects

The side effects of Abaloparatide are moderate and well tolerated. Palpitations, headaches, nausea, dizziness, and hypercalciuria are possible side effects for patients. Orthostatic hypotension and supraventricular extrasystoles have been linked to Abaloparatide. Men with Abaloparatide treatment for osteoporosis experience are more likely to experience nasopharyngitis, arthralgia, bronchitis, and hypertension[54].

2.2.2.3 Abaloparatide Vs Teriparatide in terms of Safety and Efficacy

Abaloparatide and teriparatide demonstrate comparable efficacy in reducing non-vertebral fractures and similar cardiovascular safety profiles. Abaloparatide may have some advantages in terms of MOF (Major osteoporotic fractures) reduction, BMD gains at certain skeletal sites, and a more balanced effect on bone formation and resorption [56].

2.2.2.4 Combination therapy

Some combination therapies show promise, sequential therapy using abaloparatide followed by an antiresorptive agent currently has the strongest evidence base[57]. According to the report from investigation in 2020, starting sequential treatment with abaloparatide instead of starting with alendronate may result in roughly 25%–30% better results (in terms of fractures avoided and QALYsgained)[37],[49].When compared to alendronate monotherapy, the abaloparatide/alendronate sequence proved to be more economical for women over 60 who were at a high risk of fractures[37],[49].

2.2.2.5 Case Study

Abaloparatide significantly increased BMD at multiple skeletal sites compared to placebo. Lumbar spine: 12.1% increase at 18 months; Total hip: 3.9% increase at 18 months; Femoral neck: 3.6% increase at 18 months. The BMD increases were similar across different age groups, including women 80 years and older. Abaloparatide significantly reduced the risk of new vertebral fractures compared to placebo. There were numerical reductions in nonvertebral fractures with Abaloparatide compared to placebo, though not statistically significant in all subgroups.In women aged 80 years and older, Abaloparatide was associated with numerical (but not statistically significant) reductions in vertebral and nonvertebral fracture risk compared to placebo [56][58].

2.2.3 Romosozumab

Romosozumab, sold under the brand name Evenity, is a monoclonal antibody used to cure osteoporosis in postmenopausal women at extreme risk of fracture or patients who are intolerant of other treatments[59].Evenity, received its first global approval on January 8, 2019, for the management of osteoporosis in patients at extreme risk of fracture. It was later approved by the

FDA on April 9, 2019, specifically for postmenopausal women at increased risk of fracture. Romosozumab promotes bone modeling and has a dual effect by activating bone formation and inhibiting bone resorption. With this unique mechanism of action, romosozumab treatment results in a rapid and significant increase in BMD, which is greater than that seen with bisphosphonates, denosumab, or parathyroid hormone (PTH) analogs[60].

Romosozumabpredominantly promotes modeling-based bone growth in the cancellous and endocortical surfaces. Modeling occurs when osteoblasts start bone formation on inactive bone surfaces, whereas transforming osteoblast activity is dependent on bone resorption caused by previous osteoclast activity. Romosozumab reinforces bone microarchitecture by enhancing trabecular structure and increasing bone density [61], [62], [63].

Romosozumab is a humanized monoclonal antibody(IgG2) that binds to and inhibits sclerostin. Sclerostin is an osteocyte-derived protein that inhibits the Wnt signaling pathway, which is important for bone formation. By inhibiting sclerostin, Romosozumab removes this inhibition on the Wnt-β-catenin pathway, eventually leading to increased bone formation. This stimulates bone modeling, a process where new bone is formed without prior bone resorption[61], [62], [63].

2.2.3.1 Pharmacokinetics

Romosozumab is given as a monthly subcutaneous (SQ) injection of 210 mg, regardless of body weight.

Absorption: The drug reaches peak plasma concentration (Cmax) of 22.2 ± 5.8 µg/mL approximately 5 days (range 2-7 days) after administration[64], [65], [66].

Distribution: The estimated volume of distribution at steady state is 3.92 L.

Metabolism: The exact metabolic pathway is not fully characterized, but as a monoclonal antibody, it is expected to be catabolized into amino acids and shorter peptides, similar to the metabolic pathway for human immunoglobulin G[66].

Elimination: Romosozumab has an estimated systemic clearance of 0.38 mL/kg/h and a half-life of 12.8 days after three monthly doses[66].

Nonlinear pharmacokinetics: Romosozumabdisplays nonlinear pharmacokinetics. As the dose increases, clearance declines, and drug exposure rises at a greater rate relative to the given dose [64], [66].

2.2.3.2 Adverse effects

Romosozumab, a medication used to treat osteoporosis, has several reported adverse effects. The most common side effects include joint pain, headache, and reactions at the injection site, such as pain, swelling, and redness. More serious adverse effects include,

Cardiovascular Risks: Romosozumab carries a boxed warning for an increased risk of heart attack, stroke, and cardiovascular death. Patients with a history of these conditions, particularly within the past year, are advised to avoid using romosozumab[58].

Hypocalcemia: This medication can lower calcium levels in the blood, potentially leading to muscle spasms, numbness, or tingling. Patients with pre-existing low calcium levels should have these corrected before starting treatment[67].

Osteonecrosis of the Jaw (ONJ): Although rare, romosozumab can cause severe jaw bone problems, particularly following dental procedures. A dental exam is recommended before starting treatment[58].

Atypical Femur Fractures: Unusual stress fractures of the thigh bone have been reported, often preceded by prodromal pain in the affected area[58].

Allergic Reactions: Severe allergic reactions, including skin rashes, hives, and swelling of the face or throat, can occur[67].

2.2.3.3 Combination therapy

Combination therapy involving romosozumab, particularly with other osteoporosis medications like denosumab, has been explored to optimize treatment outcomes for patients with severe osteoporosis.

A study investigated the effectiveness of adding romosozumab to ongoing denosumab treatment in postmenopausal women with severe osteoporosis. The study found that the combination resulted in significant increases in bone mineral density (BMD) at the lumbar spine compared to denosumab alone. Specifically, the combination therapy increased bone formation markers and spine BMD, suggesting that romosozumab can enhance the effects of denosumab in certain patients[68].Romosozumab is often used as part of a sequential treatment strategy, where it is followed by an antiresorptive agent such as alendronate or denosumab. This approach helps maintain or further increase the bone density gains achieved with romosozumab. For instance, a study showed that transitioning from romosozumab to alendronate resulted in a significantly lower risk of new vertebral fractures compared to alendronate alone[69][70].

2.2.3.4 Case Study

The case studies provided by the National Osteoporosis Guideline Group (NOGG) and the Royal Osteoporosis Society (ROS) offer insights into the use of romosozumab for treating severe osteoporosis. Anne (age: 65) presented with severe pain and a wedge fracture at T8. Despite a previous wrist fracture, she had not been treated for osteoporosis.Her risk factors included a low BMI, smoking, and a family history of osteoporosis. Her FRAX score indicated a high risk of major osteoporotic and hip fractures.Management discussions highlighted her high risk of further vertebral fractures, suggesting romosozumab as a suitable treatment option due to her severe osteoporosis and recent fracture history. Maria (age:74), with a history of rheumatoid arthritis and vertebral fractures, was identified as having a higher fracture risk than her FRAX score suggested. Despite her cardiovascular risk, she opted for romosozumab over teriparatide due to the convenience of administration and her personal health history[71].

3 Specific Bioactive Collagen Peptides

Bioactive collagen peptides have shown promise as a treatment for osteoporosis by improving bone mineral density (BMD) and supporting overall bone health. Bioactive collagen peptides stimulate osteoblasts, the cells responsible for bone formation, to increase the synthesis of bone components, such as collagen. They also reduce the activity of osteoclasts, which are involved in bone resorption, and slow down bone-degenerating enzymes[72][73]

Long-term supplementation with specific bioactive collagen peptides has been shown to significantly increase BMD in the spine and femoral neck. Studies have reported increases of up to 4.2% in the spine and 7.7% in the femoral neck. These improvements in BMD contribute to enhanced bone stability and reduced fracture risk[72][74] A study involving postmenopausal women with reduced BMD demonstrated that daily intake of 5 grams of specific bioactive collagen peptides over four years led to a steady improved in BMD and T-scores, with no reported fractures during the study period[75].Bioactive collagen peptides are available in various forms, such as powders, capsules, and tablets. They are typically taken as a daily supplement and can be combined with other osteoporosis treatments like calcium, vitamin D, bisphosphonates, or teriparatide for synergistic effects[73][74].

4 New Therapeutic possibilities

PEPITEM

PEPITEM, or Peptide Inhibitor of Trans-Endothelial Migration, is a naturally occurring peptide that has shown promise as a new therapeutic for osteoporosis and other disorders characterized by bone loss. It was first identified by researchers at the University of Birmingham in 2015[76]. Researchers identified PEPITEM as a bioactive 14-amino acid peptide cleaved from 14-3-3ξ15 that regulates monocyte migration into non-bone tissues during inflammation. They investigated PEPITEM's ability to directly influence the remodeling of bones under homeostatic conditions, as well as its therapeutic efficacy in models of excess bone loss [77].

Recent studies have demonstrated that PEPITEM can be used as a novel and early clinical intervention to reverse the impact of age-related musculoskeletal diseases, such as osteoporosis, by enhancing bone mineralization, formation, and strength, and reversing bone loss in animal models[76][77][78].

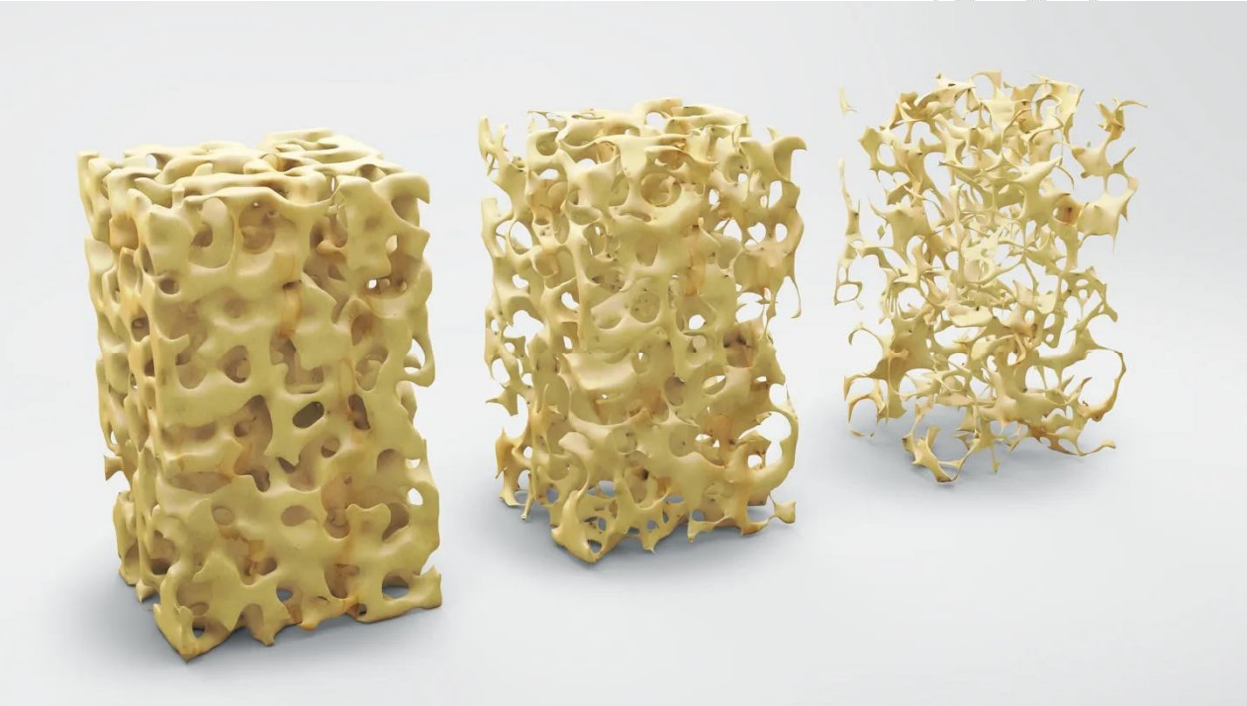

Figure 2 Effect of PEPITEM on the bone mineralization, formation, strength and density [76]

PEPITEM acts straight on osteoblasts, the cells responsible for formation of bone, via NCAM-1 signaling, promoting their maturation and new bone formation. This process leads to enhanced bone mineralization and an increase in bone strength and density (Figure 1), comparable to current standard osteoporosis treatments like bisphosphonates and parathyroid hormone (PTH). Unlike these existing therapies, PEPITEM does not affect the ability of osteoclasts, the cells that break down bone tissue, to resorb damaged or weak bone tissue, which allows for normal bone remodeling[76].Research has shown that PEPITEM can limit bone loss and improve bone mass in animal models of menopause, a common trigger for osteoporotic bone loss, and reduce bone damage in models of inflammatory bone disease, such as arthritis. These findings are supported by studies using human bone tissue, where PEPITEM significantly increased the maturation of osteoblasts and their ability to produce and mineralize bone tissues[77]

Since PEPITEM does not interfere with osteoclast's ability to resorb damaged or weak bone tissue, potentially reducing side effects related to disrupted bone remodeling[76]

5 Conclusion

Peptides and proteins have emerged as powerful anabolic and catabolic agents in the fight against osteoporosis, offering a targeted approach to bone health. As anabolic agents, certain peptides like parathyroid hormone (PTH) analogs (teriparatide and abaloparatide) and Proteins (romosozumab) stimulate bone formation by enhancing osteoblast activity, leading to improved bone density and strength. These agents are particularly valuable for patients with severe osteoporosis or those who have not reacted to other treatments, as they directly promote bone growth. On the other hand, peptide such as Calcitonin Salmon and protein such as denosumab function as catabolic agents by inhibiting bone resorption. By targeting and neutralizing RANKL, a key protein involved in osteoclast formation and activity, denosumab effectively slows down the breakdown of bone tissue, helping to preserve bone density and reduce fracture risk. The dual roles of peptides and proteins in both stimulating bone formation and counteractingon bone loss, highlight their versatility and effectiveness in osteoporosis treatment. Bioactive collagen peptides offer a promising and well-tolerated option for improving bone health and managing osteoporosis, especially in postmenopausal women and the aging population.PEPITEM, in particular, has been demonstrated to enhance bone mineralization, formation, and strength, comparable to existing treatments like bisphosphonates and parathyroid hormone (PTH).

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