Osteoporosis therapies and their mechanisms of action (Review)

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Abstract. Osteoporosis is a common disease that affects millions of patients worldwide and is most common in menopausal women. The main characteristics of osteoporosis are low bone density and increased risk of fractures due to deterioration of the bone architecture. Osteoporosis is a chronic disease that is difficult to treat; thus, investigations into novel effective therapeutic methods are required. A number of studies have focused on determining the most effective treatment options for this disease. There are several treatment options for osteoporosis that differ depending on the characteristics of the disease, and these include both well-established and newly developed drugs. The present review focuses on the various drugs available for osteoporosis, the associated mechanisms of action and the methods of administration.

Contents

1. Introduction

Osteoporosis is a bone disorder in which the balance between bone resorption and bone formation is disrupted, resulting in an increase in bone resorption that decreases bone mineral density (BMD) (1). The World Health Organization (WHO) defines osteoporosis as a 'progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture' (2,3). Osteoporosis is a common disease, affecting ~200 million patients worldwide, and by 2020, an estimated 10-14 million individuals would be affected by osteoporosis in the USA (1,4-6). Osteoporotic fractures can be alleviated by pharmacological treatment. Current osteoporosis treatments are either anti-resorptive, bone-forming or dual-acting (including both types of treatment) (5,7). Anti-resorptive drugs include bisphosphonates, anti-receptor activator of NF-κB (RANK) ligand (RANKL) antibodies (Denosumab), selective estrogen receptor modulators (SERMs) and calcitonin (3,5,7). Bone-forming drugs include parathyroid hormone (PTH) and PTH-related protein (PTHrP) (3,5,8). An example of a dual-acting drug is Romosozumab (3,5). The present review highlighted the causes of osteoporosis and the mechanisms of action underlying the drugs used to treat this disease. In addition, the present study details an approach to drug development that has the ability to treat osteoporosis in a more effective manner.

2. Consideration of targets in osteoporosis

The WHO criteria for determining osteoporosis is a reduction in BMD of ≥2.5 standard deviations (SD) below the average value for young healthy adults, as assessed via dual-energy X-ray absorptiometry (DXA) (9-14). This result is expressed as a T-score, and a low T-score (<-2.5) is an indicator of osteoporosis (12,13).

Osteoporosis is affected by several factors, including age and sex, and is divided accordingly into primary and secondary osteoporosis. Primary osteoporosis includes post-menopausal osteoporosis (type 1), which is characterized by a decreased production of estrogen that induces bone loss. On the other hand, secondary osteoporosis is caused by disease or drug exposure (type 2), and is characterized by reductions in bone function often due to malabsorption, glucocorticoid use, hyperparathyroidism, hypogonadism or excessive alcohol consumption (3,9,10,15,16).

Risk factors. Osteoporosis is influenced by multiple factors. Representative causes and risk factors for osteoporosis include, but are not limited to, increasing age, post-menopause, hormones, genetics, ethnicity, calcium levels, body weight, exercise, poor nutrition, early menopause, lifestyle habits, chronic disease, rheumatoid arthritis, vitamin D deficiency, smoking and alcohol abuse (9,17-20).

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Diagnosis. Osteoporosis is a disease that has no major symptoms unless a fracture occurs (9,17,21). However, it has previously been demonstrated that individuals aged ≥65 years and postmenopausal women begin to lose bone density due to several risk factors, including low calcium uptake, smoking, alcohol abuse, certain medications and ethnic background. These risk factors are indicative for BMD measurements (9,12,17,22). BMD T-scores are used for diagnosis, where T-scores >-1.0 SD denote normal bone mass; T-scores between -1.0 and -2.5 SD are defined as osteopenia; and T-scores <-2.5 SD are indicative of osteoporosis (9,12,13,17,22).

Bone remodeling. Bone mass is maintained by continuous bone remodeling through bone formation by osteoblasts and bone resorption by osteoclasts (23-25). Bone remodeling is affected by growth factors, hormones and cytokines, which regulate osteoclast and osteoblast activity (23,24). The regulation of osteoclast activity, differentiation and survival is critical in bone remodeling, whereby RANK, the corresponding ligand RANKL and decoy receptor osteoprotegerin (OPG) are key factors (23,26,27).

Osteoclasts. Osteoclasts differentiate from hematopoietic stem cells, and are activated by macrophage colony-stimulating factor and RANKL to attach to bone and begin resorption (3,28-30). Activated osteoclasts induce bone resorption through bone mineral dissolution and bone degradation via proteolytic enzymes and hydrochloric acid secretion (3,23,29,31-33). The main proteolytic enzymes released from osteoclasts are cathepsin K and MMP9 (3,34,35). These enzymes are released in response to PTH, and osteoclasts activated by PTH release bone minerals into the bloodstream (3,24). Furthermore, the RANK-RANKL interaction activates additional signaling pathways, such as TNF-receptor associated factor 6 (TRAF6), MAPK, NF-κB, AKT, JNK and ERK, and increases the expression of genes associated with osteoclastogenesis (3,23,24,28-30).

Osteoblasts. Osteoblasts differentiate from mesenchymal stem cells (MSCs), produce hydroxyapatite and enable bone formation through mineralized tissue formation (36-38). The mechanism of bone formation is classified into two types: Endochondral ossification and intramembranous ossification (3,39). Endochondral ossification is an essential process for the formation and growth of long bones, healing of bone fractures and formation of cartilage by chondrocytes (40,41), while intramembranous ossification is essential for rudimentary bone formation and bone fracture healing (42). Osteoblasts interact with signaling molecules, including Runt-related transcription factor 2 (Runx2), osterix, activating transcription factor 4 and the activator protein 1 family (3,43-45). In particular, Runx2 levels are increased by bone morphogenetic proteins (BMPs), Wnt levels, receptors for lipoprotein receptor-related protein 5 and 6 (LRP5/6) and frizzled (FZD)-related protein. Consequently, osteoblasts form and promote bone formation by synthesizing an extracellular matrix to maintain bone mass while inhibiting or increasing bone resorption (3,46,47). Osteoblasts also produce RANKL, which promotes osteoclast differentiation, as previously described (48,49).

Osteocytes. Osteocytes are the most common cells in mature bone. Unlike osteoclasts that survive for ~12 days and osteoblasts that survive for about 100 days, osteocytes live in the bone matrix >10 years (50-52). Osteocytes are derived from MSCs through osteoblast lineage differentiation and are the final differentiated form of osteoblasts that do not divide. Only 10-20% of all osteoblasts differentiate into osteocytes. In mature bones, osteocytes are located in specific spaces called lacunae and canaliculi, and produce several proteins that affect bone remodeling (52-56). Osteocytes promote bone formation by releasing nitric oxide, prostaglandin E2 and ATP, and suppress bone formation by releasing sclerostin, Dickkopf-related protein 1 and FZD-related protein 1. In addition, osteocytes activate osteoclastogenesis by releasing RANKL. Sclerostin is expressed only in osteocytes, which acts as a ligand in the Wnt signaling pathway, activates canonical Wnt signaling, binds to LRP5/6 receptors and inhibits bone formation (52,54,55,57,58).

OPG. OPG is a decoy receptor for RANKL and competes with RANK for binding to RANKL; therefore, OPG inhibits bone resorption by blocking the binding between RANK and RANKL. Furthermore, OPG serves as a decoy receptor for TNF-related apoptosis-inducing ligand (TRAIL), which induces osteoclastogenesis by increasing TRAF6 and NF-κB signaling, and the expression of nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) (59,60).

Vitamin D. Vitamin D is a group of fat-soluble secosteroids that increase the intestinal absorption of calcium, magnesium and phosphate (61,62). Vitamin D has two main forms: D2 (ergocalciferol) and D3 (cholecalciferol). D2 is extracted from plant sources and cannot be produced by humans, while D3 is mainly synthesized in the human skin and is ingested through animal foods, such as fish oil (63-66).

Vitamin D changes its structure several times during the digestion process, and finally becomes the activated form calcitriol, which enhances serum calcium levels by inhibiting parathyroid gene expression and parathyroid cell proliferation through binding to vitamin D receptor (VDR) (61,63,66). Calcitriol acts directly on three organ targets to maintain serum calcium levels (61,62). The first target organ is the intestine, where calcitriol stimulates intestinal calcium absorption; the second is the kidneys, where calcitriol along with PTH encourages renal distal tubular reabsorption of calcium; and the third target is bone (61-66).

Calcitriol mobilizes calcium from the bone in a process that requires PTH. When calcium levels in serum decrease, PTH-dependent calcitriol activation occurs, promoting the formation and differentiation of osteoclasts (67-70). Activation of PTH-dependent calcitriol also induces the secretion of RANKL, which in turn induces the mobilization of calcium from the bone. Vitamin D activates this signaling pathway through VDR, and VDR signaling acts primarily on osteoblasts rather than osteoclasts, directly acting on the expression of RANKL, which is important for osteoclast production and increased bone resorption (71-73). Vitamin D also inhibits mineralization by increasing the levels of pyrophosphate and osteopontin.

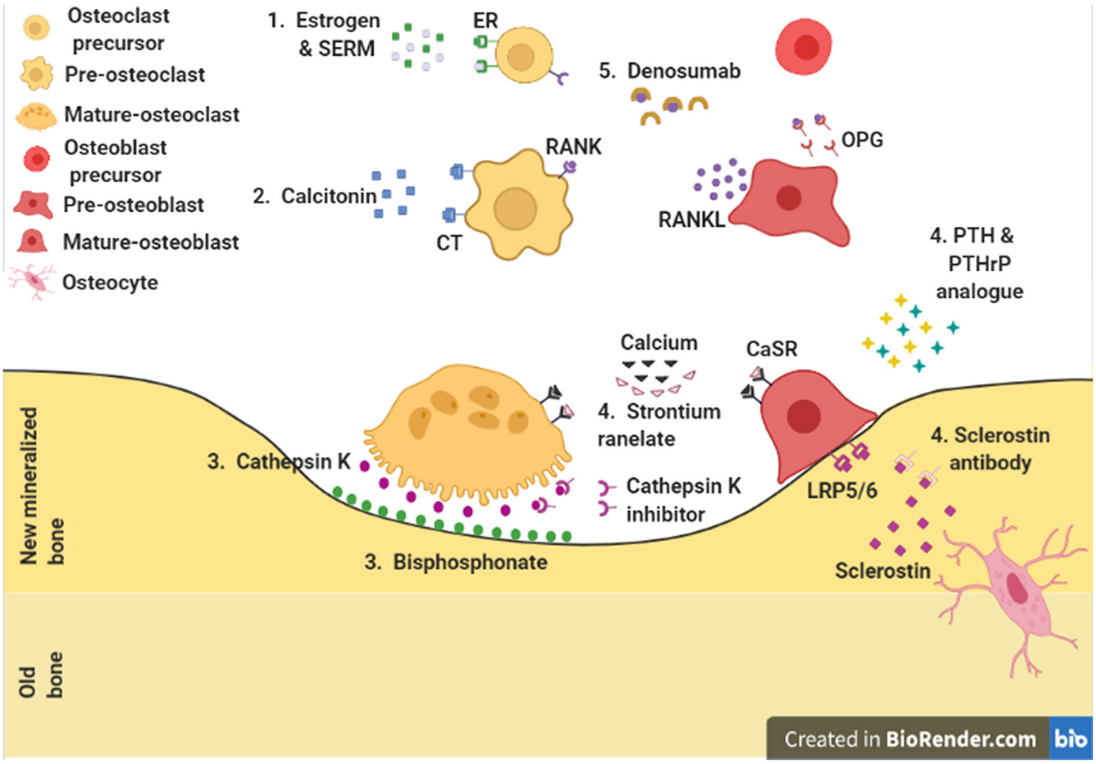

Figure 1. Pharmacological action sites for osteoporosis. 1. Pre-osteoclast: Estrogen and SERMs. 2. Osteoclast: Calcitonin. 3. Bone resorption site: Cathepsin K inhibitor and bisphosphonates. 4. Osteoblast: Strontium ranelate, PTH and PTHrP analogues, and anti-sclerostin antibody. 5. Osteoclast and osteoblast: Denosumab. ER, estrogen receptor; SERM, selective estrogen receptor modulator; CT, calcitonin receptor; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; CaSR, calcium sensing receptor; LRP5/6, lipoprotein receptor-related protein 5 and 6; PTH, parathyroid hormone; PTHrP, PTH-related protein; OPG, osteoprotegerin.

3. Pharmacological therapy for osteoporosis

A number of drugs and therapeutic methods have been evaluated for the treatment of osteoporosis (Fig. 1). Since osteoporosis is caused by an imbalance between bone formation and bone resorption, drugs for treating osteoporosis have been developed accordingly (Table I). To initiate pharmacological treatment, the main purpose of which is to lower the risk of osteoporotic fractures, it is necessary to determine the patient's current condition and T-score and DXA are used as diagnostic techniques (9,74-77).

Anti-resorptive agents

Bisphosphonates. Bisphosphonates are considered as the first-line pharmacological treatment for osteoporosis. There are several types of bisphosphonates, and their basic action is to attach to the bone and induce osteoclast apoptosis, thereby inhibiting bone resorption and increasing BMD (Table II) (9,17,78,79). Bisphosphonates are stable analogs of pyrophosphate and have a P-C-P bond that provides binding affinity to hydroxyapatite. As osteoclasts begin to resorb bones covered with bisphosphonates, the released bisphosphonates reduce the ability of osteoclasts to form wrinkled boundaries and produce protons necessary for bone resorption (3,17,80-85).

Bisphosphonates are classified into two types: Nitrogen-containing bisphosphonates (NBPs) and non-nitrogen-containing bisphosphonate (NNBPs; Table II) (78,80,86). NBPs inhibit the farnesyl pyrophosphate synthase enzyme in the mevalonate pathway, which disrupts protein prenylation and causes cytoskeletal abnormalities in osteoclasts, resulting in the release of osteoclasts from the bone (78,80,87-89). Alendronate, risedronate, ibandronate, zoledronate, neridronate and pamidronate are typical NBPs (78,80). As NNBPs do not contain nitrogen, they have a different mechanism of action compared with NBPs. NNBPs are exchanged for one half the ATP in terminal pyrophosphates and are metabolized after being incorporated intracellularly by osteoclasts. The metabolites, which act as ATP analogs, are then used instead of ATP and interfere with cell metabolism, consequently inducing osteoclast apoptosis (78,80,86,87). Etidronate, clodronate and tiludronate are typical NNBPs (80). Regardless of the type, bisphosphonates have a central carbon atom, but the length and structure of the side chains vary. These differences determine their affinity for specific skeletal sites (17,20,90,91). For example, alendronate has a high binding affinity to bone but is slow acting (91), while risedronate has a low binding affinity to bone and its effect appears rapidly due to its high diffusion ability (20,90).

Bisphosphonates are administered as oral tablets or intravenous injections; oral tablets are preferred, but in case of adverse effects, intravenous injections are used instead. Common adverse effects of the oral administration of bisphosphonates are dysphagia, abdominal pain, nausea, flatulence, constipation or diarrhea, acid regurgitation, taste distortion, esophageal ulcers and gastritis (9,17,92,93). Relatively rare adverse effects include atypical femoral fractures (AFFs), osteonecrosis of the jaw (ONJ), influenza-like symptoms,

Table I. Summary of pharmacological drugs used for osteoporosis.

A, Anti-resorptive drugs

Drug class	Mechanism of action	Name	Method of administration	Side effects	(Refs.)
NBP	Inhibition of FPPS enzyme, inhibition of the mevalonate pathway	Alendronate, risedronate, ibandronate, zoledronate	Oral	Dysphagia, nausea, constipation/diarrhea, gastritis, flatulence	(9,17,79,81,93)
NNBP	ATP derivative formation, induction of osteoclast apoptosis	Etidronate, clodronate, tiludronate	Oral, IV	AFF, ONJ, acidregurgitation, hypocalcemia, esophageal ulcers	(9,15,74,76,87)
RANKL inhibitor	Competitive binding to RANKL, osteoclast inactivation and apoptosis	Denosumab	SC	ONJ, AFF, musculoskeletal pain, gastrointestinal symptoms	(17,29,50,93,102,103)
SERMs	Binding to ER by acting in a similar manner to estrogen, induction of apoptosis of osteoclasts	Raloxifene, bazedoxifene, lasofoxifene, tamoxifen	Oral	Stroke, venous thromboembolic disorder, muscle cramps	(17,102,109,110)
ERT	Estrogen binding to ER promotes FASL transcription, induction of apoptosis of osteoclasts	Estrogen	Tablet, insert pill, patch	Breast cancer, heart disease, stroke, venous thromboembolic disorders	(79,91,96,102,105)
Calcitonin	Calcitonin binding to CT on osteoclasts, regulation of the CREB pathway	Calcitonin	Oral, intranasal spray	Hypocalcemia, nasal adverse reaction, anti-calcitonin antibody formation, prostate cancer	(111-114)
Cathepsin K inhibitor	Binding to cathepsin K and inhibition of function, reduction of collagen degradation by cathepsin K	Balicatib, odanacatib, ONO-5334	Oral	AFF, stroke, pycnodysostosis	(115-119,121,122)
Strontium ranelate	Binding to calcium sensing receptors instead of calcium, osteoclast inhibition and induction of apoptosis	Protelos®, Osseor®	Oral	Cardiovascular disorder, venous thromboembolic disorder, myocardial infarction	(45,126,128,129)

B, Bone-formation drugs

Drug class	Mechanism of action	Name	Method of administration	Side effects	(Refs.)
PTH	PTH binding to PTH1R on osteoblasts, increased bone formation by anabolic effect	Teriparatide	SC	Dizziness, headache, nausea, leg cramps, osteosarcoma	(145-149,154-156)
PTHrP	PTHrP binding to PTH1R on osteoblasts, increased bone formation by anabolic effect	Abaloparatide	SC	Gastrointestinal symptoms, dizziness, myalgia, injection site reaction, osteosarcoma	(148,157-162)

Table I. Continued.

Dual-action drugs					
Drug class	Mechanism of action	Name	Method of administration	Side effects	(Refs.)
Anti-sclerostin antibody	Degradation of sclerostin, increased Wnt signaling	Romosozumab, blosozumab	SC, IV	Stroke, cardiovascular disorder, myocardial infarction	(163,164,166,167)

NBP, nitrogen-containing bisphosphonate; FPPS, farnesyl pyrophosphate synthase; NNBP, non-nitrogen-containing bisphosphonate; IV, intravenous; AFF, atypical femoral fracture; ONJ, osteonecrosis of the jaw; RANKL, receptor activator of NF-κB ligand; SC, subcutaneous; SERM, selective estrogen receptor modulator; ER, estrogen receptor; ERT, estrogen replacement therapy; FASL, Fas ligand; CT, calcitonin receptor; CREB, cAMP-response element binding protein; PTH, parathyroid hormone; PTH1R, PTH-1 receptor; PTHrP, PTH-related protein.

hypocalcemia, uveitis and episcleritis (9,17,92,94-96). The most common adverse effects associated with the stomach and digestion are alleviated by reducing the number of doses, or changing to intravenous administration or pre-prandial administration. Rare adverse effects are alleviated by reducing the dose or changing the time between doses, since bisphosphonates continue to be effective even if they are stopped after the first administration (9,48,69-71). Despite common adverse effects, bisphosphonate is an ideal treatment option for patients with early osteoporosis if the administration method is followed up carefully (1,9,74,97).

Denosumab. Denosumab is the first fully human monoclonal antibody that competitively binds to human RANKL, thus preventing the interaction between RANK and RANKL, and inhibiting the RANK/RANKL signaling pathway. Therefore, it inhibits osteoclast activity and differentiation, and consequently inhibits bone resorption, thus inhibiting osteoclast function (3,17,28,49,92,98,99).

Denosumab is injected subcutaneously into the thigh or abdomen. Unlike bisphosphonates, it is not considered as a first-line treatment for osteoporosis. Denosumab is usually prescribed instead of bisphosphonates for patients with renal failure (78,96). To confirm the efficacy of denosumab, a study was conducted called 'Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months' (FREEDOM), which revealed an increase in BMD and a decrease in bone turnover rate in the denosumab group compared with those in the placebo group (5,17,100).

The FREEDOM study also highlighted the adverse effects of long-term denosumab treatment, which were similar to those associated with bisphosphonates, including ONJ, AFFs, hypocalcemia, musculoskeletal pain and gastrointestinal symptoms (9,78,92,101). Unlike bisphosphonates, denosumab also weakens the immune system. As denosumab targets RANK-RANKL interactions, lymphocytes requiring RANK-RANKL interactions are affected, resulting in decreased lymphocyte activity and increased risk of infection (92,101,102). Furthermore, unlike bisphosphonates, denosumab loses its efficacy rapidly after cessation of administration. If adverse effects occur, denosumab administration can be stopped immediately; however, the associated osteoporosis-suppressing effects also disappear rapidly (78,98,102,103).

Estrogen replacement therapy (ERT). Estrogen is the primary sex hormone secreted by women, and estrogen secretion decreases as menopause begins. However, in osteoporosis, estrogen regulates osteoclast apoptosis. Estrogen binds to estrogen receptor α, which translocates to the nucleus and binds the Fas ligand (FasL) transcription site to promote FasL transcription. FasL subsequently binds to Fas, a receptor present on the surface of pre-osteoclasts, inducing cleavage of caspase 8 and promoting osteoclast apoptosis (78,101,104).

Hormone replacement therapy (HRT) is similar to ERT, but instead uses progestin in combination with estrogen. ERT or HRT is administered as tablets, patches on the skin or insertion of estrogen pills under the skin (78,101,104). Long-term use of HRT and ERT exhibit adverse effects; HRT increases the risk of breast cancer, heart disease, stroke and venous thromboembolic disorders, while ERT increases the risk of endometrial cancer, stroke and venous thromboembolic disorders (1,90,95,104-107). ERT is selectively used in menopausal women and is not considered a first-line therapy for osteoporosis. ERT or HRT should be discontinued upon adverse health effects; however, discontinuation increases the risk of osteoporosis (78,101).

SERMs. SERMs are used to reduce adverse effects caused by the long-term use of estrogen. SERMs are nonsteroidal drugs that bind to estrogen receptors and exert selective estrogenic activity depending on the type of cell or tissue. SERMs function in a similar manner to estrogen, without any adverse effects on the breast or endometrium. Commonly used SERMs include raloxifene, bazedoxifene, lasofoxifene and tamoxifene (78,101).

SERMs increase the risk of stroke, thromboembolic disorders and muscle cramps (52,65,76). Thus, they are contraindicated for use in premenopausal women with osteoporosis, while they are considered a first-line therapy for postmenopausal women with osteoporosis (78,101,108,109).

Calcitonin. Calcitonin is a 32-amino acid hormone secreted by thyroid C cells. The three main functions of calcitonin are:

Table II. Classification of bisphosphonates.

A, NBPs

Drug name	Molecular formula	Indication	Potency relative to etidronate (Unit)	(Refs.)
Alendronate	$C_4H_{13}NO_7P_2$	Paget's disease, osteoporosis in men and postmenopausal women, glucocorticoid induced osteoporosis	100-1,000	(90,176)
Risedronate	$C_7H_{10}NNaO_7P_2$	Paget's disease, osteoporosis in men and postmenopausal women, glucocorticoid induced osteoporosis	1,000-10,000	(90,176)
Ibandronate	$C_9H_{22}NNaO_7P_2$	Osteoporosis in postmenopausal women	1,000-10,000	(90,176)
Zoledronate	$C_5H_{10}N_2O_7P_2$	Paget's disease, osteoporosis in men and postmenopausal women, glucocorticoid induced osteoporosis	>10,000	(90,176)
Neridronate	$C_6H_{16}NNaO_7P_2$	Paget's disease, osteogenesis imperfecta, osteoporosis	100	(90,176)
Pamidronate	$C_3H_9NNa_2O_7P_2$	Hypercalcemia of malignancy, Paget's disease, osteolytic lesions of multiple myeloma	100	(90,176)

B, NNBPs

Drug name	Molecular formula	Indication	Relative potency (Unit)	(Refs.)
Etidronate	$C_2H_8O_7P_2$	Paget's disease, heterotopic ossification following total hip replacement	1	(81,176)
Clodronate	$CH_4Cl_2O_6P_2$	Osteolytic bone metastases, hypercalcemia of malignancy, transient osteoporosis of the hip	10	(81,176)
Tiludronate	$C_7H_9ClO_6P_2S$	Paget's disease, osteoporosis	10	(81,176)

NBP, nitrogen-containing bisphosphonate; NNBP, non-nitrogen-containing bisphosphonate.

i) To absorb calcium into the bones; ii) to inhibit calcium reuptake in the kidneys; and iii) to inhibit calcium reuptake in the small intestine. Thus, for osteoporosis treatment, calcitonin functions by storing calcium in bones. The majority of cells require calcium, which is necessary for multiple functions within cells. Among the different tissues that store calcium, bone stores the largest quantity of calcium by combining it with phosphoric acid to form hydroxyapatite (110-112).

The actions of calcitonin are opposite to those of PTH; PTH increases the concentration of blood calcium, whereas calcitonin decreases it (111,112). Calcitonin binds to the calcitonin receptor on osteoclasts and regulates transcription through the cyclic adenosine monophosphate (cAMP)/protein kinase A(PKA)-cAMP-response element binding protein pathway (110-112).

Methods for calcitonin administration include injection, oral formulation and intranasal spray. Two types of calcitonin are used in therapy: Human and salmon calcitonin. Salmon calcitonin is used more often due to its high affinity for human calcitonin receptors. Calcitonin treatment is usually considered a second-line therapy for osteoporosis, and it is used when first-line therapy is ineffective or intolerable (78,101,113). Calcitonin also exhibits adverse effects, such as hypocalcemia, nasal adverse reactions, formation of calcitonin antibodies and prostate cancer (9,101). If adverse effects appear following the use of calcitonin treatment, it must be replaced with alternate osteoporosis therapies.

Cathepsin K inhibitors. Cathepsin K is a member of the papain-like cysteine protease family and is highly expressed in osteoclasts. When osteoclasts are activated, cathepsin K, residing in the lysosomes of osteoclasts, is released into the resorption lacuna, initiating bone resorption (114,115). During bone resorption, osteoclasts form a structure called the sealing zone, which is a dynamic actin-rich structure that defines the resorption region. Subsequently, osteoclasts secrete several molecules, including proteases, to break down bone material for resorption (114-116). The bones are composed of a mineralized organic matrix consisting of 30% organic components and 70% inorganic components. The majority

of organic components are composed of type 1 collagen, while the inorganic components are mainly composed of hydroxyapatite (114,115,117). There are two types of collagen, types 1 and 2, which form a triple helix structure with two α1 chains and one α2 chain. Due to this structure, collagen resists proteolysis by proteases, such as MMP9 and serine protease. By contrast, cathepsin K efficiently cleaves collagen and any telopeptides to form collagen monomers (114,115,117-119), thus being an important marker of bone resorption and an ideal therapeutic target. When cathepsin K is inhibited, bone resorption activity of osteoclasts is suppressed, resulting in increased BMD (114-117).

Cathepsin K inhibitors include balicatib, odanacatib and 2H-Pyran-4-propanoic acid (114,119-121), which are administered orally. Unlike other bone resorption inhibitors, they inhibit the activity of osteoclasts, rather than reducing the number. Cathepsin K inhibitors are good anti-resorptive agents, but the associated adverse health effects are yet to be fully established. Reported adverse effects include increased risk of stroke, AFF and pycnodysostosis (114,118,121,122). The stability of cathepsin K inhibitors is also yet to be elucidated; therefore, further studies on the adverse effects and stability of cathepsin K inhibitors are required (101,118,120,123,124).

Strontium ranelate. Osteoblasts and osteoclasts have calcium sensing receptors (CaSRs), and their activity changes based on extracellular calcium concentration. Calcium activates various cellular pathways (40,44,125). In osteoblastic cells, elevated extracellular calcium levels activate signaling pathways, including phospholipase C (PLC), protein kinase C (PKC), ERK, JNK, cAMP and PKA (3,29). The ERK pathway increases the proliferation of osteoblastic cells, while the AKT pathway inhibits the apoptosis of osteoblastic cells by increasing survival signals (3,29). Additionally, calcium increases the expression of insulin-like growth factor (IGF)-1 and IGF-2, thereby increasing the proliferation of osteoblastic cells and inducing differentiation by increasing the expression of cyclooxygenase 2 and prostaglandin E2 (125,126). In osteoclasts, when CaSR is activated by high levels of extracellular calcium, PLC and NF-κB are activated, thus inducing the apoptosis of osteoclasts (125,126).

Strontium, with an atomic number of 38, is located just below calcium on the periodic table (127,128). The nucleus of strontium is approximately the same size as that of calcium; thus, cells absorb strontium instead of calcium and transport it to bone or tooth enamel (127,128). Although the mechanism of action of strontium ranelate has not been clearly identified, the characteristics of strontium and the reported research (127,128) suggest that it enters the cell through CaSRs of osteoclasts and osteoblasts, and acts in a similar manner to calcium (125,127,128). Therefore, strontium ranelate increases the differentiation and proliferation of osteoblasts, and the activated osteoblasts produce OPG, which reduces the activity of osteoclasts. Furthermore, it acts directly on the CaSRs of osteoclasts and increase their apoptosis (125,127,129).

Strontium ranelate is administered orally. Due to its adverse effects, strontium ranelate is considered a second-line therapy, and is administered when other osteoporosis therapies cannot be used or are ineffective (78,101). Common adverse effects include cardiovascular disorders, venous thromboembolism, myocardial infarction and symptoms of the nervous system. Rarely reported adverse effects include allergic reactions, such as drug rash with eosinophilia and systemic symptoms syndrome. Adverse effects associated with the heart are particularly severe. Therefore, it is recommended that strontium ranelate is administered only to patients with severe osteoporosis. It is not recommended for patients with severe renal impairment, thrombophlebitis, ischemic heart disease, a history of peripheral artery disease, cerebrovascular disease or hypertension (101,128,130-132).

Mutant RANKL. Mutations within the TNF-like core domain of RANKL have been reported for creating a novel therapy for osteoporosis. The identification of RANKL as the final effector in the pathogenesis of osteoporosis has led to an improved understanding of bone remodeling. When RANKL binds to its receptor (RANK), osteoclastic differentiation and activation are initiated. RANKL is a member of TNF superfamily, which is a group of cytokines involved in cell proliferation and cell death consisting of 19 multimeric ligands interacting with cognate receptor molecules, the majority of which require trimerization to initiate their signaling cascade (133). Ligands belonging to the TNF superfamily are mostly type II transmembrane glycoproteins, containing a C-terminal, receptor-interacting ectodomain, a transmembrane domain and an N-terminal intracellular tail. The extracellular domain is either cleaved by the proteolytic activity of metalloproteases or produced by alternative splicing (133). Three-dimensional structures of TNF-α, TRAIL and RANKL (alone and in complex with their respective receptors) have revealed remarkably similar overall structures that comprise unique conserved elements involved in receptor binding (134). Ko *et al* (135) and Jang *et al* (136) proposed a strategy using a RANKL variant as a competitive inhibitor for RANKL/RANK signaling. They suggest that this RANKL variant activates leucine rich repeat containing G protein-coupled receptor 4 (LGR4) signaling, which competitively regulates RANK and acts as an immunogen that induces anti-RANKL antibody production, demonstrating a strategy in the development of general immunotherapy. The RANKL variant did not bind RANK in osteoclast progenitor cells, but activated LGR4 through the GSK3-β signaling pathway, thereby suppressing the expression and activity of activated T cell cytoplasmic NFATc1 during osteoclastogenesis (Fig. 2). The aforementioned RANKL variant generated high levels of RANKL-specific antibodies, blocked osteoclastogenesis and inhibited osteoporosis in ovariectomized mouse models. Generated anti-RANKL antibodies demonstrated a high inhibitory effect on osteoclastogenesis *in vivo* and *in vitro*. In addition, Liu *et al* (137) demonstrated that immunization with a RANKL mutant generates an inter-species anti-RANKL antibody, which blocks the interaction between RANKL and its receptor, and further prevents the formation of osteoclasts and improves the bone density in rats with ovariectomy (OVX). Furthermore, the development of an unnatural amino acid into a RANKL vaccine has been proposed as a therapeutic approach to inhibit RANKL activity (138). An anti-RANKL vaccine, Y234pNO_2Phe, was constructed by substituting a single tyrosine residue (Tyr234) in murine RANKL with p-nitrophenylalanine (pNO_2Phe), and it was demonstrated that Y234pNO_2Phe induced a high titer antibody response

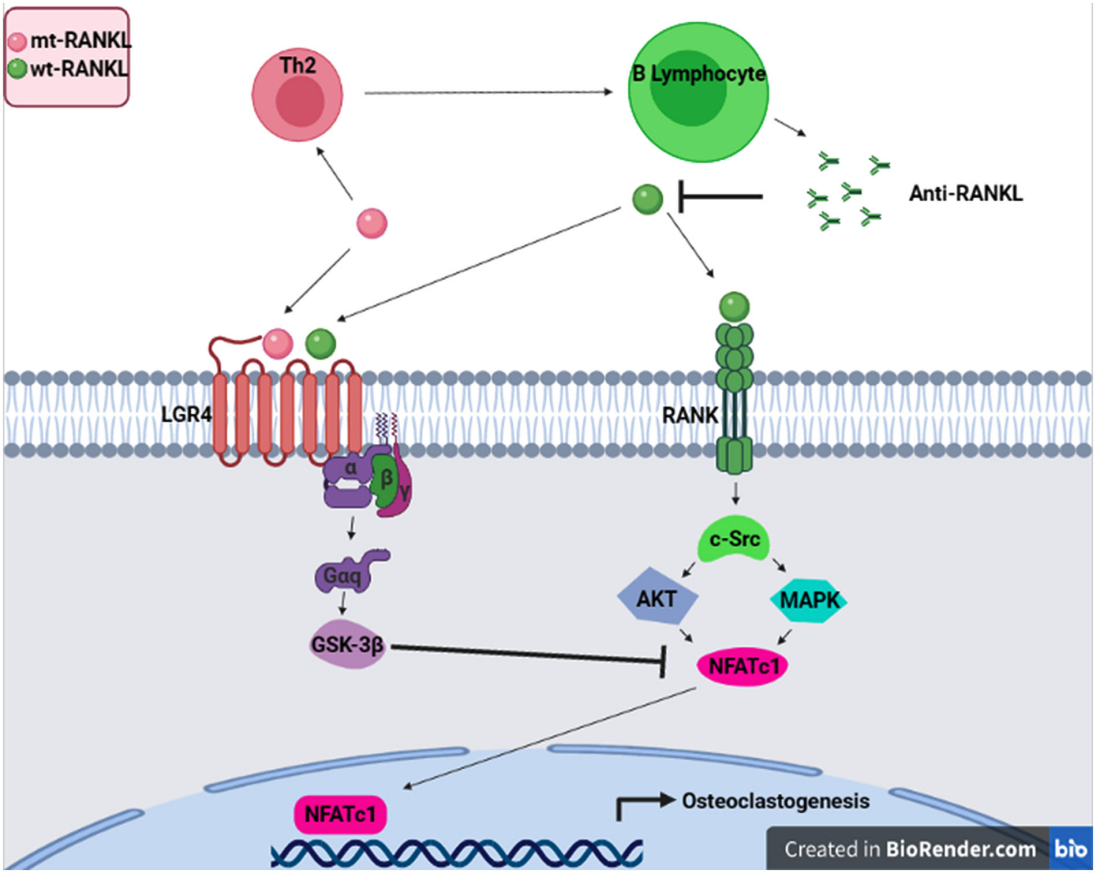

Figure 2. Schematic diagram of mutant RANKL and inhibitory effect against RANKL during osteoclastogenesis. RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; LGR4, leucine rich repeat containing G protein-coupled receptor 4; mt, mutant; wt, wild-type; NFATc1, nuclear factor of activated T-cells cytoplasmic 1.

in C57BL/6 mice and prevented OVX-induced bone loss in mice (138). The potential advantage of a vaccine-type approach to RANKL inhibition compared with that of antibody-based approaches is that patients who discontinue denosumab experience rapid increases in bone remodeling and an increased risk of multiple vertebral fractures. It is possible, although not clearly demonstrated, that this vaccine approach may not induce rapid high-turnover bone loss, either by causing more durable RANKL inhibition or by allowing a more gradual resumption of remodeling when vaccinations are discontinued. It would be reasonable to evaluate this vaccine approach for its ability to minimize the risk of high-turnover bone loss in situations where vaccinations and boosters are discontinued.

Non-coding RNA. Long non-coding RNAs (lncRNAs) represent a group of non-protein-coding RNA transcripts that have been reported to play pivotal roles in various biological functions such as gene expression, cell proliferation and differentiation (139). As a 'bridge' between DNA and protein, RNA serves a complex regulatory role. In eukaryotic cells, protein-coding RNA (mRNA) only accounts for ~2% of the genome, and the remaining transcripts are categorized as non-protein-coding RNAs (133). Unlike ribosomal RNA and transfer RNA, which are well known, other non-coding RNAs were previously considered to be transcriptional 'noise' (140). However, a recent study by Zhu *et al* (141) revealed that lncRNAs serve a vital role in regulating bone and cartilage development and remodeling processes. Research on microRNAs (miRNAs/miRs) and lncRNAs in the context of osteoporosis is limited. Often, there are conflicting results in the literature, such as miR-223 having the ability to both promote and inhibit osteoclastogenesis. Wijnen *et al* (142) suggested that miRNAs provided both positive and negative cross-talk between different regulatory pathways, thereby leading to the aforementioned phenomenon. Another potential explanation is that miRNA is present in different clinical specimens. For example, Mandourah *et al* (143) found that while both miR-122-5p and miR-4516 were suitable biomarkers for osteoporosis, miR-122-5p was detectable in serum, while miR-4516 was found in plasma (143). A large cohort study of 682 women found that there was no association between bone parameters and circulating levels of miRNAs, although these results changed after age adjustment. The authors suggested that this observation could be due to the fact that age was also strongly associated with the serum levels of the 32 miRNAs they selected. These factors may be associated with fragility fracture and low BMD in patients with osteoporosis, and may provide new insights into the modulation and potential treatment of osteoporosis.

Bone formation therapies

PTH analogue. PTH is an 84-amino acid peptide hormone that is synthesized in the parathyroid glands and regulates serum calcium concentration. PTH function is mediated by PTH-1

receptor (PTH1R), which is a G protein-coupled receptor (GPCR) expressed in osteoblasts and oocytes (144-146). When PTH1R is stimulated, it activates several GPCR-related signaling pathways, such as the cAMP/PKA, PLC/PKC and ERK signaling pathways. Furthermore, PTH regulates the Wnt signaling pathway by downregulating sclerostin, a Wnt antagonist (145-149). The effects of PTH are divided into anabolic and catabolic effects. The anabolic effect of PTH increases the differentiation and growth of osteoblasts, thereby increasing bone formation, while its catabolic effect increases bone resorption indirectly, since osteoclasts are activated by RANKL secreted by osteoblasts (146-148).

PTH analogues are administered in a continuous or intermittent manner. When a PTH analogue is administered, markers of bone formation are initially increased, and those of bone resorption are activated at a later point; the period in which bone formation is higher than bone resorption is called the anabolic window, during which maximum bone formation occurs. After the anabolic window period, bone resorption gradually increases (150-152). PTH analogues are not recommended as first-line therapy for osteoporosis due to their high cost and difficulty of administration by subcutaneous injections. Adverse effects of PTH analogues include dizziness, headache, nausea and leg cramps. In addition, in animal experiments, osteosarcoma was reported to be induced based on the duration of the treatment; therefore, the administration of PTH analogues should be limited to 2 years (153-155).

PTHrP analogue. PTHrP, a member of the PTH family, is secreted by MSCs. PTH and PTHrP share 8 of the first 13 amino acids, have similar secondary structures, an overall homologous sequence and bind to the same receptor (147,156,157). PTH1R has two conformations: i) G protein-dependent RG conformation; and ii) a G protein-independent R0 conformation. The two conformations activate the same signaling pathway, yet demonstrate different response patterns depending on the activated conformation (158-160). Long-lasting signaling was observed when the R0 conformation was activated, whereas short-lasting signaling was observed when the RG conformation was activated. Since anabolic and catabolic effects are activated as a long-acting signal in the R0 conformation, the anabolic effect is low; whereas in the case of the RG conformation, the anabolic effect is high with a strong signal that lasts for a short time. The binding affinities of the ligands for these two conformations are different. PTHrP analogues have a higher affinity for the RG conformation than that of PTH analogues. Thus, PTHrP analogues are expected to exert an improved anabolic effect than that of PTH analogues (144,147,159-161).

The adverse effects of PTHrP analogues are similar to those of PTH analogues, including gastrointestinal complaints, injection-site reactions, dizziness and myalgia. Furthermore, a mouse model demonstrated that PTHrP analogs were associated with osteosarcoma and osteoblastoma, similarly to the observations with PTH analogues. Thus, PTHrP analogue administration is limited to 2 years (153-155,158).

Dual-action therapy

Anti-sclerostin antibody. Sclerostin is a glycoprotein secreted by osteocytes; it functions as an antagonist of BMP and suppresses the canonical Wnt signaling pathway. Sclerostin interacts with pro-BMP7 and mature BMP7 to increase the intracellular accumulation of BMP7, leading to its degradation. Thus, sclerostin inhibits the BMP7 signaling pathway (162,163). The canonical Wnt signaling pathway is activated by the binding of a Wnt ligand to a receptor complex composed of LRP5/6 and FZD receptors. FZD mediates the recruitment of axin to form a complex that inhibits β-catenin phosphorylation by GSK-3β. Non-phosphorylated β-catenin then accumulates in the cytoplasm, resulting in its nuclear translocation, and thereby triggers the transcription of genes involved in bone formation. It also induces the internalization of LRP5/6, which forms a complex with axin and adenomatous polyposis coli protein, which then degrades phosphorylated β-catenin (144,162-164). Anti-sclerostin antibody treatment removes sclerostin from the Wnt signaling pathway, thus activating the canonical Wnt signaling pathway, and consequently promoting bone formation and inhibiting bone resorption. β-catenin inhibits osteoclastogenesis by increasing the production of OPG in osteoblasts and by regulating the RANK/RANKL/OPG signaling pathway. Therefore, activation of the canonical Wnt signaling pathway not only increases bone formation but also decreases bone resorption (144,162,164).

Anti-sclerostin antibody treatment is administered via subcutaneous injection, and the most common adverse effects are stroke, cardiovascular events and myocardial infarction. Furthermore, Wnt signaling is associated with cancer, which has been reported as an adverse effect in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study (144). Long-term anti-sclerostin antibody treatment, therefore, is not recommended, since it poses a high risk to the heart and may cause cancer (144,165,166).

Combination therapy. Since pharmacological therapies for osteoporosis have limitations, several studies have been conducted to determine more effective therapies. An example of which is combination therapy, which is expected to exert a synergistic effect by using either two anti-resorptive drugs or an anti-resorptive drug with an anabolic drug.

In several studies, combination therapy was evaluated using existing drugs. The PTH and alendronate study used a combination of PTH and alendronate, and demonstrated no increase in BMD compared with that of the individual use of PTH or alendronate. Another study used a combination of PTH and SERMs, and also demonstrated no increase in BMD. By contrast, a combination of denosumab and teriparatide slightly increased BMD (76,101,167-169). Another study reported that teriparatide can be used alone or in combination with denosumab and abaloparatide (170). Previous studies have indicated that PTH and PTHrP-related protein analogues, whether as monotherapy, in combination or in sequence with anti-resorptive agents, serve an important role in the management of osteoporosis (170). Since the benefit of combination therapy is only a slight increase in BMD, it is generally not recommended for osteoporosis due to its combined adverse effects and increased cost. Therefore, combination therapy is limited to patients with high risk of fractures or when other therapies are ineffective.

Sequential therapy. Since combination therapies are associated with more adverse effects than clear advantages, studies

to identify other effective therapies, such as sequential therapy, have been conducted. Sequential therapy has been used to overcome the limitation of prolonged treatment time, which is a common problem with osteoporosis drugs.

In the denosumab and teriparatide transitions in postmenopausal osteoporosis (DATA-Switch) study, BMD increased in the spine and hips upon switching to denosumab after teriparatide treatment (100,171). In the Abaloparatide Comparator Trial in Vertebral Endpoints study, switching from abaloparatide to alendronate increased BMD and maintained lowered fracture risk (165,171,172). In the FRAME study, switching from romosozumab to denosumab also maintained a lower fracture risk. In an active-controlled fracture study in postmenopausal women with high risk of osteoporosis, switching from romosozumab to alendronate increased BMD and decreased non-vertebral fracture risk (171-175). As demonstrated in a number of studies, sequential therapy is effective against osteoporosis as it increases BMD compared with the effects of single sustained therapy. However, it has adverse effects, most of which appear to be similar to that of single therapies.

4. Conclusions

Osteoporosis, a chronic and difficult-to-cure disease, occurs naturally with age. As the lifespan of a person increases, so does the incidence of osteoporosis and the length of disease (1,9). Therefore, effective long-term treatment options for osteoporosis are required. Among the various treatments for osteoporosis that are currently in use, pharmacological therapy is the most efficient and accessible, and has been rigorously studied (9,10). Currently used therapies include those that inhibit bone resorption, promote bone formation and dual-action therapies (9,17). Pharmacological therapies are used in patients with osteoporosis to reduce the risk of fracture and increase BMD, but their use is limited by adverse effects, which are determined by multiple factors, including the patient's nutritional status, genetic factors and past medical history (7-9,13,17). To reduce these adverse effects, studies on individual variability, such as treatment time, concentration and timing of the administration of drugs, as well as drugs' mechanisms of action, such as osteoclast inhibition and osteoblast growth promotion, have been conducted (13,17,20). In addition to single therapies with drugs, combination therapy and sequential therapy are under investigation to treat osteoporosis more effectively. However, it is not yet possible to completely cure osteoporosis, and there are serious adverse effects develop due to the long-term use of the current drugs. Therefore, there is a need to develop novel drugs that have the ability to effectively treat osteoporosis while minimizing adverse effects, regardless of variable patient-related factors.

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Availability of data and materials

Not applicable.

Authors' contributions

BK, YJC and WL were responsible for project conceptualization. BK and YJC were responsible for writing and original draft preparation:. WL was responsible for writing, reviewing and editing the manuscript, and creating the figures. BK and YJC were responsible for the assessment of all the raw data. WL was responsible for project supervision and administration. BK, YJC and WL were responsible for funding acquisition. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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