

CLINICAL REVIEW

The Role of Receptor Activator of Nuclear Factor- κ B (RANK)/RANK Ligand/Osteoprotegerin: Clinical Implications

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Context: Receptor activator of nuclear factor- κ B ligand (RANKL), receptor activator of nuclear factor- κ B (RANK), and osteoprotegerin (OPG) play a central role in bone remodeling and disorders of mineral metabolism.

Evidence Acquisition: A PubMed search was conducted from January 1992 until 2007 for basic, observational, and clinical studies in subjects with disorders related to imbalances in the RANK/RANKL/OPG system.

Evidence Synthesis: RANK, RANKL, and OPG are members of the TNF receptor superfamily. The pathways involving them in conjunction with various cytokines and calcitropic hormones play a pivotal role in bone remodeling. Several studies involving mutations in the genes encoding RANK and OPG concluded in the discovery of a number of inherited skeletal disorders. In addition, basic and clinical studies established a consistent relationship between the RANK/

RANKL/OPG pathway and skeletal lesions related to disorders of mineral metabolism. These studies were a stepping stone in further defining the role of the RANK/RANKL/OPG pathway in osteoporosis, rheumatoid arthritis, bone loss associated with malignancy-related skeletal diseases, and its relationship to vascular calcifications. Subsequently, the further understanding of this pathway led to the development of new therapeutic modalities including the human monoclonal antibody to RANKL and recombinant OPG as a target for treatment of postmenopausal osteoporosis and multiple myeloma.

Conclusions: The RANK/RANKL/OPG system mediates the effects of calcitropic hormones and, consequently, alterations in their ratio are key in the development of several clinical conditions. New agents with the potential to block effects of RANKL have emerged for treatment of postmenopausal osteoporosis and malignancy-related skeletal disease. (*J Clin Endocrinol Metab* 92: 4514–4521, 2007)

DISCOVERY OF THE receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system as a key mediator of bone remodeling has been invaluable to our basic understanding of this process and has bridged basic research to the treatment of multiple clinical conditions. Dysregulation of the RANK/RANKL/OPG system has been implicated in the pathophysiology of multiple bone remodeling disorders including osteoporosis, glucocorticoid-induced bone loss, multiple myeloma, and rheumatoid arthritis. The discovery of this system has led to recognition of the genetic basis of various skeletal disorders and the development of new therapeutic approaches, including a monoclonal antibody to RANKL for the treatment of postmenopausal osteoporosis.

Bone Remodeling Cycle

Bone is a dynamic tissue that constantly remodels in response to mechanical stresses and hormonal changes (1).

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Abbreviations: JPD, Juvenile Paget's disease; OPG, osteoprotegerin; PDB2, early-onset Paget's disease of bone; RANK, receptor activator of nuclear factor- κ B; RANKL, RANK ligand; sRANKL, soluble RANKL; TRAIL, TNF-related apoptosis-inducing ligand.

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Bone remodeling occurs within discrete units throughout the skeleton called bone remodeling units and involves a dynamic equilibrium between osteoclastic bone resorption and osteoblastic bone formation. Each remodeling cycle begins with the transformation of a quiescent bone surface to a bone resorptive surface (2, 3). Osteocytes are thought to play a principal role in initiating bone remodeling by conveying local signals to osteoblasts and osteoclasts on bone surface via a canalicular system (4–8). The principal function of osteoclasts is to resorb matrix by creating resorption pits (Howship's lacunae) (9). Bone resorption within a given bone remodeling unit ends with apoptosis of the osteoclasts and is followed by coupling signals sent to osteoblasts to appear at the resorption cavities. Osteoblasts then synthesize bone matrix, which mineralizes extracellularly after deposition by osteoblasts.

Regulatory Mechanisms of Bone Remodeling

Osteoclasts are multinucleated cells originating from granulocyte and macrophage-colony-forming unit hematopoietic stem cells (9). Osteoclastic cell activity is regulated by various cytokines including IL-1, -6, and -11, colony stimulating factors, and calcitropic hormones including PTH, 1,25-dihydroxyvitamin D3, and calcitonin.

Recently, members of the TNF and TNF-receptor super-

family, RANKL, RANK, and OPG, were shown to play a key role in the formation and activation of osteoclasts in conjunction with various cytokines and calciotropic hormones. Experimental studies have demonstrated that RANKL is expressed by osteoblasts and bone marrow stromal cells, whereas its receptor RANK is expressed in preosteoclasts and other cells of this lineage (10) (Fig. 1). The interaction between RANKL and RANK stimulates osteoclastic formation and differentiation (11–14) by activation of several transcription factors that regulate osteoclastogenesis (15, 16). OPG is produced by osteoblasts and acts as a decoy receptor that competes with RANKL for RANK (17, 18). This interaction inhibits osteoclastic proliferation and differentiation and consequently prevents bone resorption (Fig. 1).

Clinical Conditions Associated with Alterations in the RANK/RANKL/OPG System

The discovery of the RANK/RANKL/OPG system and its interaction with various cytokines and calciotropic hormones in the regulation of osteoclastogenesis have led to further understanding of the pathophysiology of several disorders of mineral metabolism.

Postmenopausal osteoporosis

Since discovery of the RANK/RANKL/OPG system as a final pathway in osteoclast formation and differentiation, several investigators have confirmed the key role of this pathway in the pathogenesis of postmenopausal osteoporosis. *In vitro* experiments in human osteoblastic cell lines have shown a dose- and time-dependent increase in OPG mRNA in response to 17β -estradiol (19–21). This up-regulation of OPG is expected to decrease the interaction of RANKL with RANK *in vivo* and, consequently, reduce osteoclastic bone resorption. Furthermore, the administration of OPG to ovariectomized rats was shown to prevent bone loss (22). Moreover, in experiments using dual-color flow cytometry, human bone marrow cells from untreated early postmenopausal women exhibited a greater expression of RANKL compared with estrogen-treated postmenopausal women (23). Recent attempts to measure serum levels of RANKL and OPG and correlate these with bone turnover markers and

bone mineral density in postmenopausal women in various populations have yielded mixed results (23–26). These contradictory findings may relate to differences in study design, methodology, or other aspects influencing the measurements of these factors (see below).

Glucocorticoid-induced osteoporosis

Glucocorticoid use, a major secondary cause of osteoporosis, alters both osteoblastic bone formation and osteoclastic bone resorption. Recently, the critical role of the RANK/RANKL/OPG system in the pathogenesis of glucocorticoid-induced bone disease has been described. Systemic glucocorticoids can stimulate RANKL expression by osteoblasts and inhibit OPG synthesis with resulting enhancement of osteoclast proliferation and differentiation (27). This interaction may explain the accelerated bone resorption observed early after initiation of glucocorticoid therapy. Clinical studies of patients treated with glucocorticoids for both Crohn's disease and chronic glomerulonephritis demonstrated a significant increase in the serum RANKL/OPG ratio (28, 29). This change correlated with increased levels of urinary and serum markers of bone resorption and with a fall in bone mineral density. Whether glucocorticoid-induced alterations in the RANK/RANKL/OPG system also influence osteoblastic activity remains unclear.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory condition associated with progressive destruction of the articular synovial lining (30). T cell invasion of the synovium plays a crucial role in the obliteration of the articular cartilage and adjacent bone. Furthermore, fibroblast-like synovial cells have been shown to play a role in this process (30, 31). Until recently, the pathophysiological mechanism of systemic and localized bone loss in rheumatoid arthritis was unclear. It has been demonstrated that T cells express RANKL (32, 33) and that there is overexpression of RANKL mRNA in the synovium of rheumatoid arthritis patients at the site of the bone resorption (34). Elevated serum levels of soluble RANKL and OPG have been demonstrated in patients with rheumatoid

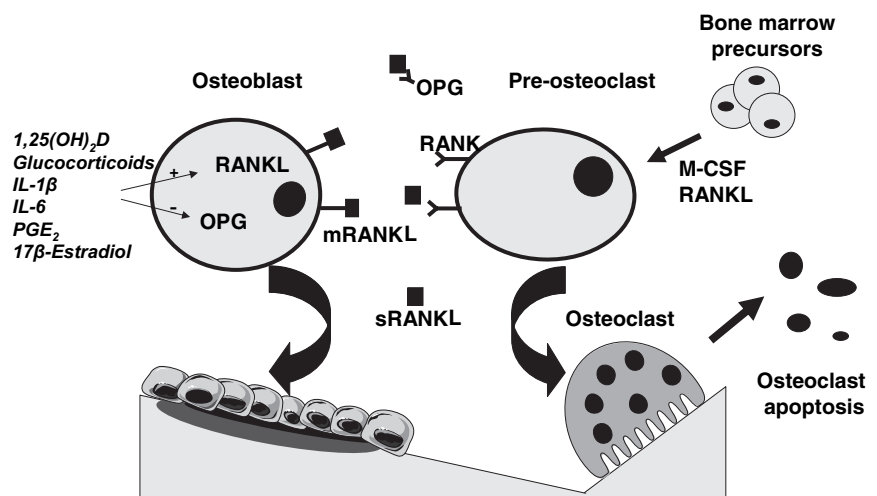


FIG. 1. Regulatory mechanisms of bone remodeling: role of RANK, RANKL, and OPG in osteoclast activation. On the left are shown factors that modulate RANKL/OPG balance: +, stimulatory; -, inhibitory. $1,25(\text{OH})_2\text{D}$, 1,25-dihydroxyvitamin D₃; M-CSF, macrophage-colony stimulating factor; mRANKL, membranous RANKL; PGE₂, prostaglandin E₂.

arthritis, and these factors normalize after treatment with anti-TNF therapy (35).

Multiple myeloma

Multiple myeloma is associated with osteolytic lesions that were initially attributed to an unidentified factor named osteoclastic activating factor (36). Osteoclastic activating factors were shown to be produced by myeloma cells in response to various cytokines including IL-1, IL-6, and TNF- α (37). Recently, an imbalance in the RANK/RANKL/OPG system was suggested as an alternative mechanism for enhanced osteoclastogenesis in bone loss associated with multiple myeloma. Derangements in the RANK/RANKL/OPG system may be due to alterations in RANKL production and/or increased lysosomal degradation of OPG (38). Increased RANKL expression in multiple myeloma may be due to its direct production by myeloma cells or its indirect production through the increased synthesis of IL-7, which then overexpress RANKL in T lymphocytes (38–41).

Vascular calcification

Atherosclerotic disease is prevalent in the aging population. Several studies have suggested an association between atherosclerosis, vascular calcification, and osteoporosis (42–48). Traditionally, vascular calcification has been considered a passive process involving increased extracellular calcium and phosphorus concentrations. Recently, it has been suggested that this process may be a more active one, similar to that of bone formation (44, 49). This concept is supported by the expression of the osteoblastic transcription factors in calcifying vascular smooth muscle cells (50, 51). An imbalance

in the RANK/RANKL/OPG system has been suggested as responsible for the calcification process of atherosclerotic plaques (45, 52, 53).

Experimental studies have shown the presence of calcified deposits in the aorta and renal arteries in homozygous OPG knockout mice (54). Furthermore, increased expression of RANK and RANKL has been seen in the calcified arteries of this animal model (55). A plausible mechanism is that OPG opposes the activity of the RANK/RANKL system, thereby inhibiting the process of vascular calcification. The rise in serum OPG concentration detected with advanced age may be an adaptive mechanism to control vascular calcification (43).

Genetic disorders

Discovery of the RANK/RANKL/OPG system has led to recognition of several rare genetic disorders of mineral metabolism (Table 1). Inactivating mutations in the OPG gene (TNFRSF11B) and activating mutations in the RANK gene (TNFRSF11A) have been identified.

OPG gene. Mutations in the OPG gene can cause abnormalities in the ligand-binding properties of OPG, resulting in its inactivation and a disorder with diverse phenotypic presentations (55). Juvenile Paget's disease (JPD) is a rare autosomal recessive disorder that presents in early childhood with bone deformities, fractures, hearing deficits, and dental abnormalities of variable severity. The disorder can be due to an inactivating mutation in the OPG gene (TNFRSF11B), localized to chromosome 8q24.2 (56). Missense mutations in the cysteine residues of OPG are predicted to interfere with its

TABLE 1. Genetic diseases related to the RANK/RANKL/OPG system

Diseases	Mutations and mode of inheritance	Clinical manifestations	Radiological findings
JPD	Chromosome 8q24.2 Deletion of TNFRSF11B (OPG gene) Autosomal recessive	Failure to thrive Hearing deficit Delayed gross motor skills Bone deformities Hypercalciuria	Osteopenia of long bones Coarse bone trabeculae Skull involvement
	PDB2	Chromosome 18q21–22 27-bp insertion mutation in TNFRSF11A (RANK gene) Autosomal dominant	Dental and hearing defects in young age Characteristic involvement of the mandible and maxilla Pain and deformities of lower limbs and pelvis Transient hypercalcemia (immobilization)
Expansile skeletal hyperphosphatasia		Chromosome 18q21–22 15-bp tandem duplication in TNFRSF11A (RANK gene) Autosomal dominant	Early deafness Premature loss of teeth Broad and flattened face Generalized skeletal pain Swelling and deformities, especially in the fingers Episodic hypercalcemia
	Familial expansile osteolysis	Chromosome 18q21.1-q22 18-bp tandem duplication in TNFRSF11A (RANK gene) Autosomal dominant	Deafness in childhood Dental defects Bone pain, deformities, and fractures in limb bones

ligand-binding domain and are responsible for the most severe phenotype of JPD (55). In more intermediate forms of JPD, missense mutations in residues other than cysteine are present in the ligand-binding region of the OPG. In addition, an insertion-deletion in exon 5 of this gene has been associated with a milder form of the disease. All of these mutations lead to unopposed activation of RANK to varying degrees, resulting in enhanced osteoclastogenesis and consequently increased bone turnover.

RANK gene. RANK is encoded by the TNFRSF11A gene located on chromosome 18. Mutations in the RANK gene that disrupt the signal peptide region of the protein result in the lack of normal cleavage of the signal peptide and an increase in RANK-mediated signaling. These activating mutations result in three different phenotypic presentations described below (57).

Early-onset Paget's disease of bone (PDB2) is a heterogeneous, autosomal dominant skeletal disorder characterized by bone deformities, hearing deficits, and dental problems. Skeletal manifestations begin in the late teen years and may progress later in life (58). PDB2 is due to an activating mutation in the RANK gene comprised of a 27-bp tandem duplication.

Expansile skeletal hyperphosphatasia, an autosomal dominant disorder, presents with early onset of deafness, dental defects, and accelerated bone turnover manifested by pain in the bones and episodic hypercalcemia (59). Skeletal symptoms begin before puberty and progress with episodes of exacerbation until middle age. The activating mutation in the RANK gene is caused by a 15-bp tandem duplication (60).

Familial expansile osteolysis is an autosomal dominant disorder that presents in early childhood to young adulthood with hearing deficit. Osteopenia is a common feature and dental abnormalities are uncommon. The major skeletal finding in this disorder is osteolysis followed by bony expansion due to fat deposition rather than osteosclerosis (61). The genetic abnormality is an activating mutation in the RANK gene linked to an 18-bp tandem duplication.

Assessment of Serum OPG and Soluble RANKL (sRANKL)

Assays for OPG and sRANKL in the circulation in humans have been developed. OPG is a glycoprotein that circulates as a monomer or homodimer and may be bound to RANKL (62). OPG is produced in various tissues including bone, skin, stomach, intestine, lung, heart, and placenta (18). Therefore, serum concentrations of OPG may not accurately reflect its levels in the bone milieu. Commercial ELISA detect all forms of circulating fragments of OPG (63). A PCR technique, an investigative tool, exclusively detects the homodimeric form of OPG (62).

Laboratory measurements of sRANKL are done by assay that is limited by the relative instability of serum RANKL (62, 64, 65). Physiological factors such as cyclic variation, menstrual status, age, and gender must also be considered in interpretation of RANKL assay results.

Several researchers have demonstrated that serum OPG concentrations increase with age in both women and men

(Table 2) (66). OPG levels are higher in osteoporotic women with high bone turnover than in control, nonosteoporotic, age-matched subjects (67–69). However, whether there is an association between serum OPG/sRANKL and incidence of bone fractures has been controversial, with some finding increased and others decreased fractures in association with higher levels of this ratio (70–72). The serum OPG level is affected by its renal clearance and renal function with a higher serum OPG level found in patients on chronic hemodialysis (73). Hormonal changes during pregnancy and lactation may also lower the serum OPG concentration and may be responsible for accelerated bone turnover in these conditions (74, 75). Physiological factors regulating serum RANKL concentrations have not been identified.

In summary, the clinical applications of sRANKL and OPG assays are at present limited due to methodological difficulties, circulating levels that may not reflect tissue levels, and the influences of many physiological factors (e.g. age, ethnicity, gender, renal function, and hormonal status). Although serum OPG and sRANKL determinations may be useful in cross-sectional cohort studies, their reliability in individual patients remains to be established.

Clinical Implications

Prostate cancer

OPG is a potential novel indicator for the diagnosis and early progression of prostate cancer (76–78). In one study of 104 patients with either advanced prostate cancer treated with antiandrogen therapy or newly diagnosed prostate cancer, serum OPG levels were higher than in young healthy control subjects (76). Moreover, OPG concentrations were greater in patients with advanced rather than localized disease. Furthermore, patients that responded to antiandrogen treatment, as indicated by a low serum prostate-specific antigen, were found to have significantly lower serum OPG levels. Thus, OPG may be

TABLE 2. Determinants of serum OPG and RANKL concentration

Physiological conditions	Serum OPG	Serum RANKL
Age	?	?
Pregnancy/lactation	?	?
Renal function	?	?
Disease states/clinical conditions		
Postmenopausal osteoporosis	? ↓	↑ ↓
Rheumatoid arthritis	?	↑
Multiple myeloma	↓	↑
Vascular calcifications	?	↑
Prostate cancer	?	?
Breast cancer	↔	?
Renal osteodystrophy	? ↓	?
Primary biliary cirrhosis	?	↓
Treatment		
Glucocorticoids	↓	↑
Estrogen	? ↓	↓
Aromatase inhibitor	?	?
Bisphosphonates	↔	↔

↑, Increase in serum concentration; ↓, decrease in serum concentration; ↑ ↓, unequivocal serum concentration; ↔, no significant change in serum concentration; ?, not well studied.

come a useful marker in the management of patients with advanced prostate cancer.

Multiple myeloma

Several studies have found lower concentrations of serum OPG in patients with multiple myeloma compared with controls (79–81). Moreover, the serum OPG concentrations in patients with radiographic evidence of multiple myeloma were found to be lower than in those patients without skeletal manifestations (79, 81). Serum OPG levels also correlated with the World Health Organization multiple myeloma performance status, the grading scale of skeletal morbidity in three stages of this illness, and the serum marker of bone formation, carboxyl-terminal propeptide type I procollagen (79). However, serum OPG concentrations have not been found to be associated with clinical stage or survival.

Breast cancer

OPG production by breast cancer cells is a possible mechanism to enhance tumor cell survival because OPG can inhibit TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis (82). In a cross-sectional study, baseline serum OPG concentrations were similar between breast cancer patients with and without bone metastases (83). However, serum OPG levels increased from baseline after a 12-wk treatment with an aromatase inhibitor (anastrozole) only in patients with skeletal involvement. Prospective studies are needed to verify whether there is value in measuring serum OPG concentrations to predict the presence of bone lesions in patients with breast malignancy.

Renal osteodystrophy and renal transplant

Renal osteodystrophy is a complex group of disorders characterized by either increased or suppressed bone turnover (84, 85). Serum OPG concentrations are lower in patients with adynamic bone disease, which accounts for a large percentage of the skeletal disease in this population, in contrast to those with increased bone turnover due to PTH stimulation (86). It is possible that the increased serum OPG concentrations in patients with chronic kidney disease may be an adaptive mechanism to attenuate PTH-induced bone loss. It is tempting to suggest that the serum OPG concentration may be used as a marker of bone turnover to predict the development of adynamic bone disease, but a major limitation is the decreased renal clearance of OPG in patients with renal impairment (73). Moreover, the significance of serum OPG levels after renal transplantation has not been fully explored. One study showed a rapid decline in serum OPG levels after transplantation, independent of alterations in creatinine clearance. These results suggest that serum OPG changes may have been due to direct effects of immunosuppressive medications on bone remodeling (87). Similar changes were shown in patients after cardiac transplantation, implicating serum OPG as a possible participant in the pathogenesis of bone loss in patients after solid organ transplantation (88).

Future Therapeutic Approaches to Bone Diseases

The discovery of the RANK/RANKL/OPG system has led to exploration of novel therapeutic options for the treatment of skeletal disorders. Although an elevated RANKL/OPG ratio promotes bone loss, restoring a more physiological ratio might reduce osteoclast activation and slow bone resorption. Promising strategies include recombinant OPG and human monoclonal antibody to RANKL.

Multiple myeloma and breast malignancy

In a phase I, randomized, double-blind trial, the effect of a single sc dose of human monoclonal OPG was tested in 28 patients with multiple myeloma and 26 patients with osteolytic lesions from breast carcinoma (89). The treatment rapidly decreased urinary markers of bone resorption, similar to the bisphosphonate pamidronate. A major limitation in the use of monoclonal OPG is its significantly short half-life, which limits its duration of inhibition of bone resorption to several weeks (90).

The efficacy of a human monoclonal antibody to RANKL (denosumab) compared with pamidronate was examined in a randomized, double-blind, controlled study in patients with multiple myeloma and skeletal metastasis from breast carcinoma (91). A single dose of denosumab decreased urinary and serum markers of bone resorption within 1 d of drug administration. This antiresorptive effect persisted for approximately 3 months in patients who received the highest dosage of denosumab, longer than the changes seen in the group of patients treated with pamidronate. Whether denosumab reduces the occurrence of new skeletal lesions and/or decreases bone pain in patients with multiple myeloma and skeletal metastatic disease from breast carcinoma remains to be determined.

Postmenopausal osteoporosis

In a double-blind, randomized, placebo-controlled, dose-escalation, phase I trial involving 52 healthy postmenopausal women, OPG administration significantly decreased bone resorption markers (92). The maximal fall in bone resorption markers was 4 d after a single dose of OPG and persisted for 6 wk. Another single-dose, placebo-controlled phase I trial in 49 healthy postmenopausal women determined the safety and reversible antiresorptive effect of human monoclonal antibody to RANKL (denosumab) (93). This agent caused a rapid, sustained, and dose-dependent decrease in urinary N-telopeptide after a single dose.

A phase III, double-blind, randomized, placebo-controlled trial compared the effects of denosumab to open-label oral alendronate in 412 postmenopausal women with osteopenia and osteoporosis (94). Treatment with denosumab for 12 months significantly increased the bone mineral density at the lumbar spine from 3 to 7% in a dose-dependent manner, which was comparable to the 5% increase in lumbar spine bone density in alendronate-treated patients. Bone mineral density at the total hip increased significantly from 2 to 4% comparable to an increase of 2% with alendronate. The efficacy of these drugs against the development of fractures has not yet been explored. Intermittent injections of denosumab

may circumvent the problem of poor compliance with oral bisphosphonates (95).

Two major concerns regarding treatment with human monoclonal antibodies to RANKL and recombinant OPG are the potential development of infections and the possible increased risk of malignancy due to modulation of the immune system (96). One possible mechanism for the development of malignancy is an alteration in TRAIL, which is a potent inhibitor of various tumor cells (97–99). *In vivo*, OPG can act as a decoy receptor for TRAIL and block TRAIL-induced apoptosis. Blockade of RANKL action may increase the effectiveness of OPG to block TRAIL and possibly to increase the growth of tumors. The theoretical basis for the increased propensity for infections with RANKL inhibition stems from the expression of RANK on T, hematopoietic, and dendritic cells (12, 32). Furthermore, the binding of RANKL to RANK may regulate T cell activation as well as dendritic cell function (32, 100). Inhibition of T and B cell function has been observed in RANKL-deficient mice (100). In the single-dose, controlled study of the human monoclonal antibody to RANKL in postmenopausal women, there was no change in lymphocyte counts or in the numbers of B cells, and T cells expressing CD4, CD8, and CD56 (93). In the phase III trial with denosumab, a 2% incidence of neoplasm and a 1% incidence of unspecified infection were noted after 12 months in the denosumab groups, whereas neither problem developed in subjects in the placebo group or the alendronate group. These potential complications as well as antifracture efficacy of therapies targeting the RANK/RANKL/OPG pathway should be evaluated in larger and longer clinical trials.

Conclusion

The elucidation of the RANK/RANKL/OPG system has vastly increased our understanding of the mechanisms underlying the bone remodeling process. This system plays a central role in the pathophysiological mechanisms underlying postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, osteolytic processes involved in multiple myeloma and metastatic breast carcinoma, rare inherited bone disorders, and the development of atherosclerosis. With the discovery of the RANK/RANKL/OPG system, novel therapeutic options for the treatment of skeletal disorders have emerged, including denosumab, the human monoclonal antibody to RANKL.

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