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# The Roles of Osteoprotegerin in Bone Diseases: a brief review

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*Authors*

Masoumeh Mohammadi[1*], PhD
Alireza Jalali[1], [2]MD

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[1] Sport Medicine and Knee Research Center, Milad Hospital, Tehran, Iran

[2] Health Systems Engineering Research Center, Milad Hospital, Tehran, Iran

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** Correspondence*
Sport Medicine and Knee Research Center, Milad Hospital, Tehran, Iran
P.O.Box: 1449614531
Fax: 00982188621147
Tel: +982188621147
E-mail mgm8362@gmail. com

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ABSTRACT

**Aims:** This article aims to highlight the crucial role of osteoprotegerin (OPG) in bone homeostasis and to propose it as a potential therapeutic target for common bone diseases.
**Method and Materials:** A literature review was conducted focusing on the structure, function, and regulatory effects of OPG on osteoclast activity, as well as its mechanism as a decoy receptor that inhibits osteoclast formation.
**Findings:** Evidence indicates that OPG plays a protective role against excessive bone loss by inhibiting osteoclast differentiation and activity. Its unique structure, consisting of a signal peptide and seven functional domains, enables it to act effectively in the extracellular space, maintaining bone balance.
**Conclusion:** This study revealed that OPG is a key regulator of bone metabolism and may represent a promising therapeutic target for the treatment and prevention of bone-related disorders. Increased attention to this protein could lead to innovative therapeutic strategies for managing metabolic bone disease.

**Keywords:** Osteoprotegerin, Osteoporosis, Osteogenesis imperfecta, Paget's Disease of Bone, Bone Metastasis, Osteomalacia, Rheumatoid Arthritis

## Introduction

Osteoprotegerin (OPG), meaning "bone protector," was first purified from human fibroblast culture media in 1997 by Tsuda and colleagues as an Osteoclast Genesis Inhibitory Factor (OCIF) due to its ability to resorb bone. Subsequently, Simont and colleagues, using an animal model, found that transgenic mice overexpressing OPG developed osteopetrosis and reduced osteoclast numbers. They identified OPG as an essential regulator of bone density. With increasing research on the structure and function of OPG, we now know that OPG is a secreted heparin-binding glycoprotein belonging to the Tumor Necrosis Factor (TNF) receptor superfamily that exists as a 55-62 Kilodalton (kDa) monomer or a 110-120 kDa disulfide-linked homodimer [1].

OPG is expressed and secreted by a variety of cells in the bone marrow, including osteoblasts, B cells, megakaryocytes, platelets, vascular endothelial cells, and vascular smooth muscle cells [2]. In addition to the bone marrow, OPG expression is also observed in many tissues, including the heart, kidney, liver, and spleen [3]. OPG, produced by osteoblasts, as one of the most essential ligands for Receptor activator of nuclear factor kappa-B ligand (RANKL), binds to Receptor Activator of Nuclear Factor Kappa-B (RANK) on the surface of osteoclast precursors and recruits the adhesion protein TRAF6, leading to the activation and translocation of Nuclear Factor Kappa-B (NF-κB) to the nucleus. Activation of this pathway subsequently increases the expression of c-Fos, which interacts with Nuclear Factor of Activated T cells c1 (NFATc1) to initiate transcription of osteoclast genes [4].

In addition to the NF-κB signaling pathway, other downstream pathways are triggered by RANKL activation, including the PI3K, Gαq/GS3K-β, ERK, JNK, and p38/MAPK pathways [5]. Also, binding to RANK, OPG has been shown to bind to TRAIL, thereby preventing its interaction with death receptors and blocking

TRAIL-induced apoptosis [6].

Besides RANKL and Tumor necrosis factor (TNF)-Related Apoptosis-Inducing Ligand (TRAIL) TRAIL, OPG has been shown to bind to von Willebrand factor (vWF) and is stored in Weibel-Palade (WP) bodies, which fuse with the outer membrane of endothelial cells and release their contents into the plasma upon activation [7]. Similarly, binding of the Factor VIIII (FVIII) and von Willebrand factor (VWF) complex to OPG blocks the interaction of OPG with TRAIL, suggesting a potential for the FVIII/vWF complex in tumorigenesis [8]. It has also been shown that multiple myeloma cells can bind, internalize, and degrade OPG. This process, dependent on the interaction of OPG with heparan sulfates on myeloma cells, can reduce the bioavailability of OPG, which acts as a bone resorption inhibitor [9].

In light of these findings, OPG may have a variety of roles beyond its primary role in bone health, as it is also involved in vascular biology, immune modulation, and fibrosis. It may also play a role in various diseases, including cancer and cardiovascular disease. In this article, we review the literature on the effective role of this protein in bone diseases.

## Method and Materials

### Osteoprotegerin and Osteoporosis

Osteoporosis is characterized by significant bone loss, which is indicated by the breakdown of bone mass and microstructure, resulting in weakened bones. It is a complex, multifaceted endocrine disorder. Its development depends on various internal and external risk factors that disrupt normal bone remodeling, causing an increase in catabolic activity that ultimately leads to bone loss. In healthy individuals, the cycle of bone remodeling is characterized by a close balance between bone resorption and formation. This condition can arise due to an inability to achieve optimal peak bone mass during developmental years, a relative rise in bone resorption in later life, or a relative decline in bone formation during adulthood. While osteoporosis has numerous and varied causes, a common underlying pathophysiological mechanism is the uncoupling of the bone remodeling cycle, resulting in increased bone resorption compared to bone formation [10].

The process of bone remodeling is carefully regulated to ensure bone mineral balance and integrity. The differentiation of osteoclasts is promoted by the RANKL and macrophage colony-stimulating factor (MSCF), while OPG, produced by osteoblasts and osteocytes, acts as an inhibitor [11]. Consequently, the balance of the OPG/RANKL ratio is crucial in regulating bone resorption, bone mass, and skeletal integrity [12]. Several studies have evaluated the clinical relevance of serum OPG levels and, more recently, serum RANKL in the context of postmenopausal osteoporosis. One study found a connection between low serum OPG and prevalent vertebral fractures among osteoporotic postmenopausal women [13]. Additionally, elevated serum RANKL was associated with osteoporosis and increased bone resorption [14]. Since bone resorption is governed by the relative expression and production levels of OPG and RANKL, the OPG/RANKL ratio has been demonstrated to play a significant role in bone resorption in postmenopausal women with osteoporosis [15].

Conversely, some findings appeared contradictory. It was noted that higher serum OPG levels had a negative correlation with body mass index and/or bone mineral density (BMD) [16]. Yano et al. discovered that serum OPG levels were markedly higher in osteoporotic women compared to age-matched controls, a result that has been validated in subsequent research [17]. Furthermore, Schett et al. found that low serum RANKL levels alongside high serum OPG levels were linked to the occurrence of nontraumatic fractures [18]. In this context, we performed an updated meta-analysis to thoroughly evaluate the relationship between serum OPG/RANKL levels and osteoporosis, offering a clinically relevant summary that may assist in biomarker selection for both research and osteoporosis assessment [19]. Chi et al. reported in a meta-analysis study that OPG and RANKL are important modulatory factors of bone formation and resorption, respectively, in bone turnover. OPG/RANKL ratio was associated with osteoporosis. Although the serum level of both OPG and

RANKL was not associated with osteoporosis [20].

## Osteoprotegerin and Osteogenesis Imperfecta

Osteogenesis imperfecta (OI), commonly referred to as brittle bone disease, is a hereditary condition characterized by bones that are excessively fragile and susceptible to fractures. It is characterized by a defect in the production of type I collagen, a vital protein essential for maintaining bone integrity. This defect leads to a variety of skeletal issues, including fragility, fractures, and deformities.

In earlier understanding, osteogenesis imperfecta (OI) was believed to result solely from dominant mutations in the genes responsible for type I collagen (COL1A1 and COL1A2), leading to defective type I collagen. Patients diagnosed with OI were classified into Sillence types I-IV according to their clinical characteristics [21]. However, the identification of additional rare causative genes has led to the view that OI is now a condition "associated" with type I collagen [22]. Specific genetic mutations result in OI not by impacting the type I collagen pathway but rather by affecting bone mineralization. An autosomal recessive mutation in the tumor necrosis factor receptor superfamily member 1 (TNFRSF1) gene causes Silence type VI OI. Mutations in this gene do not interfere with collagen synthesis or osteoblast differentiation, but they do promote increased bone resorption. SERPINF1 is responsible for encoding the protein pigment epithelium-derived factor (PEDF), which acts as an anti-angiogenic factor that supports the expression of osteoprotegerin [23, 24]. PEDF enhances the expression of OPG, which inhibits the maturation of osteoclasts by binding with RANKL, thus preventing RANKL from attaching to RANK. A loss-of-function mutation in SERPINF1 results in heightened differentiation and activation of osteoclasts, which is influenced by a disrupted RANKL/ osteoprotegerin system, leading to increased bone mass degradation. Thus, defects in PEDF raise the number of osteoclasts and bone resorption by altering the OPG/RANKL/RANK pathway, which ultimately causes a decrease in bone mineralization [25].

Osteoprotegerin and Paget's disease of bone

Paget's Disease of Bone (PDB) ranks as the second most common metabolic bone disorder globally, with prevalence rates ranging from 1.5% to 8.3%. This condition generally emerges later in life, especially in individuals in their late 50s, and is seen more frequently in men than in women [26]. Factors contributing to PDB likely include environmental influences and specific genetic mutations that lead to abnormal bone remodeling, which is affected by changes in osteoclast activity. PDB has a complicated genetic foundation that involves multiple genes, one of which is the TNFRSF11B gene [27].

Loss-of-function mutations involving the complete deletion of the tumor necrosis factor receptor superfamily member 11B gene have been recognized as a cause of juvenile Paget's disease [28]. This is a rare recessive condition characterized by severely disrupted bone remodeling, bone enlargement, and bone deformities that manifest during childhood and adolescence. Additionally, a partial alteration in the TNFRSF11B gene leading to the loss of a conserved aspartate at codon 192 has also been identified. There is some evidence suggesting that common polymorphisms within the TNFRSF11B gene may increase susceptibility to classical PDB in women, but not in men; however, this requires confirmation through a large-scale study [29, 30]. This gene produces the OPG protein, which regulates the development and activity of osteoclasts by counteracting the promoting effects of RANKL on osteoclast differentiation. The altered OPG cannot prevent osteoclastic resorption in a bone culture environment, indicating that it represents a loss-of-function mutation.

## Osteoprotegerin and Osteomyelitis

OsteoMyelitis (OM) is an invasive infection that affects bone or bone marrow, leading to significant disruption of bone homeostasis and resulting in osteolysis. Bone resorption in OM is not solely due to loss of activity or death of osteoblasts. Another very important factor is the dramatic increase in osteoclast differentiation and activity. In this context, it

should be remembered that osteoblasts produce two critical factors, RANKL and OPG, in the regulation of osteoclastogenesis [31].

Several etiological agents affect bone or bone marrow, severely impairing bone homeostasis and resulting in osteolysis. The most common cause is infection with Staphylococcus aureus [32]. Studies of osteomyelitis caused by Staphylococcus aureus infection have shown that osteoblasts increase the synthesis of RANKL while decreasing the production of OPG, thereby increasing the rate of osteoclastogenesis [33]. Furthermore, it has been shown that osteoclasts infected with S. aureus lead to a significant release of Prostaglandin E2 (PGE2), a molecule that can increase the production of RANKL by binding to its specific receptor Prostaglandin E2 receptor 4 (EP4) [34]. The effective interaction between PGE2 and EP4 leads to a significant increase in RANKL levels, which significantly accelerates the rate of osteoclastogenesis [35].

One of the characteristic features of OM is a strong state of oxidative stress (OS) with severe consequences on the delicate balance between osteoblastogenesis and osteoclastogenesis. In fact, oxidative stress hinders osteoblast activation and the production of OPG, resulting in heightened RANKL activity and the differentiation and activation of osteoclasts. This is evident through the rise in the RANKL/OPG ratio, which serves as a reliable measure of bone resorption intensity. Consequently, increases in this index indicate an imbalance favoring bone resorption processes that are not sufficiently countered by bone formation, and this is associated with the development of osteomyelitis [36].

## Osteoprotegerin and Bone Metastasis

A variety of preclinical and clinical studies have been conducted to investigate the role of OPG in tumor formation and cancer progression. Mechanistic research has demonstrated that OPG plays a crucial role in several key characteristics of cancer, including tumor persistence, Epithelial-to-Mesenchymal Transition (EMT), invasion, neoangiogenesis, and metastasis.

The mechanism of OPG's effect on cancer is complex, and many studies have been conducted. Among its effects is the inhibition of cell apoptosis, which increases tumor survival. According to Lane et al., OPG blocked the TRAIL-induced apoptosis of ovarian cancer cells through a mechanism reliant on αvβ3 and αvβ5 integrins [37]. Also, in inflammatory breast cancer, OPG engages with glucose-regulated protein/ immunoglobulin-binding protein (GRP78/BiP), which is a chaperone in the endoplasmic reticulum (ER) and a key regulator of the unfolded protein response, to enhance cell apoptosis and extend the lifespan of inflammatory breast cancer cells [38]. In gastric cancer, RANK facilitated the migration of cancer cells by interacting with the lipid raft core protein Cav-1 and EGFR, and this impact was reduced by OPG [39]. The function of OPG has also been detailed in relation to angiogenesis, a crucial process for the upkeep, development, and progression of tumors. Cross et al. found that the expression levels of OPG in the endothelial cells of malignant colorectal, breast, and metastatic tumors were greater than in benign tumors or normal tissues. Additionally, the external application of OPG promoted the creation of cord-like structures by endothelial cells in vitro [40]. Benslimane et al. discovered that the combination of OPG and fibroblast growth factor (FGF-2) enhanced neovascularization in vivo, which was linked to the activation of proangiogenic pathways that involve the MAPK signaling pathway, along with Akt or mTOR cascades in endothelial colony-forming cells (ECFCs) [41]. Additionally, ECFCs that were pretreated with OPG secreted stromal cell-derived factor-1 (SDF-1), leading to increased neovascularization in ischemic tissue [42].

Bone is one of the most common sites of cancer metastasis, especially for prostate, breast, and lung cancer [43]. Given the crucial role of OPG in bone homeostasis, the involvement of OPG in bone metastasis has been widely investigated.

OPG has a multifaceted role in bone metastasis. Although it is recognized for its ability to prevent bone resorption by inhibiting the RANKL pathway, which is essential for osteoclast function, it may also

unexpectedly aid in the growth of tumors in bone metastases. This paradoxical effect is linked to OPG's impact on the local RANKL gradient, which influences the behavior of osteoclasts and the survival of tumor cells.

In research focusing on benign prostatic hyperplasia, both primary and metastatic cases demonstrated that OPG mRNA expression levels were higher in metastatic tumor tissues in comparison to local tissues. The ratio of RANKL to OPG was noted to be elevated in tumors with bone metastases relative to normal prostate tissues [44]. Through the evaluation of serum OPG and RANKL levels, Elfa et al. determined that the sensitivity and specificity of serum OPG for diagnosing bone metastases in breast cancer were 59% and 92%, respectively. In comparison, the RANKL/OPG ratio exhibited sensitivity and specificity rates of 73% and 72%, respectively [45]. In the case of Hepatocellular carcinoma (HCC), Huang et al. observed that OPG non-coding RNA enhances HCC bone metastasis by lowering OPG levels, thereby fostering a bone microenvironment conducive to metastasis [46].

By reducing osteoclast activity and disrupting the tumor-osteoclast cell cycle, bisphosphonates are frequently prescribed to patients with bone metastases. Ross et al. found that the sensitization of TRAIL/OPG by zoledronic acid (ZA) in MDA-MB-231 cells responded well to TRAIL, indicating that the TRAIL/OPG cytokine system plays a role in the specific response to bisphosphonates in cancer research conducted in vitro [47]. Following a year of ZA treatment, a reduction in the RANKL/OPG ratio was noted, indicating that ZA diminished osteoclast activity by decreasing levels of RANKL and OPG [48].

## Osteoprotegerin and Osteomalacia

Osteomalacia, frequently referred to as adult-onset rickets, is a metabolic bone disorder commonly known as "soft bone disease," arising from the insufficient mineralization of bone tissue caused by a lack of vitamin D, calcium, or phosphate. This lack of minerals results in weakened and softened bones, presenting symptoms such as bone pain, muscle weakness, and a higher susceptibility to fractures. OPG may play a role in osteomalacia by affecting bone remodeling. Although the specific relationship is still under investigation, it is certain that in osteomalacia, the interaction between OPG and RANKL (another protein involved in bone remodeling), as well as other factors, may be disrupted, leading to abnormal bone turnover [49].

## Osteoprotegerin and Rheumatoid arthritis

In rheumatoid arthritis (RA), bone erosions occur due to the resorption of bone by osteoclasts at areas affected by synovitis (synovitis refers to the inflammation of the synovial membrane, a delicate tissue that lines the interior of joint cavities). Both localized and extensive bone loss have been noted in RA, suggesting that immune system activation may impact bone health. This condition, characterized by inflammation and bone damage, suggests that the interactions among the OPG/RANKL/TRAIL system and T cells may provide insight into the lesions observed [50-52].

Fadda et al. demonstrated that in patients with RA, alterations in the OPG/RANKL system, resulting in higher levels of RANKL and lower levels of OPG in the peripheral blood, may play a role in the significant bone loss and development of osteoporosis observed in these individuals. Another study indicated that RANKL knockout mice and those treated with OPG did not experience focal bone loss, despite ongoing joint inflammation. Additionally, Cohen et al. reported that the inhibition of osteoclasts by denosumab, a humanized antibody that targets RANKL explicitly, can prevent the occurrence of erosions and periarticular bone loss [53].

Recent studies suggest that the bony erosions observed in RA may be triggered by the activation of the RANKL/RANK system, which is initiated by activated T cells. The release of RANKL from activated T cells can stimulate the formation of osteoclasts. This process is further amplified by various cytokines (TNF-alpha, IL-1, and IL-17) that facilitate both inflammation and bone loss [54, 55]. In contrast, this pathway is suppressed by factors such as

OPG, IL-4, and IL-10, which are known for their anti-inflammatory properties and their ability to prevent osteoclast development. In the rheumatoid synovium, activated T cells are known to express RANKL [56]. Under certain conditions, synoviocytes have the potential to differentiate into osteoclast-like cells, especially when exposed to M-CSF and RANKL in culture [57]. This suggests that using OPG therapy to inhibit this mechanism could be advantageous for patients suffering from RA. Additionally, TRAIL, an anti-inflammatory molecule primarily recognized for inducing apoptosis in cancer cells, has been shown to have a protective function in rheumatoid arthritis (RA). Therefore, TRAIL may play a role in modulating the systemic inflammatory autoimmune response caused by the disease. Nonetheless, growing evidence suggests that it may act as a pleiotropic cytokine with dual functions. Since OPG can interact with TRAIL and inhibit its activity, it has been suggested that the OPG/TRAIL ratio could also contribute to the pathogenesis of RA [52].

## Conclusion

The function and molecular mechanisms of OPG in bone biology and related disorders have been rigorously studied over the past few decades. In addition to its role in bone ailments, significant insights into OPG's involvement in other benign conditions and the progression of cancer have been gained. OPG serves as a versatile component that can influence vascular biology, fibrosis, immune responses, epithelial-mesenchymal transition (EMT), and the apoptosis of cancer cells. As a secreted protein, OPG performs bioactive functions by influencing various cellular signal transduction pathways and modifying the local microenvironment. Moreover, the detection of secreted OPG in human blood, along with its distinctive expression pattern, offers a promising non-invasive method for diagnosing and predicting outcomes in patients, particularly those with cancer.

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## Author Contributions

MM was the principal investigator and collected the data, analyzed it, and wrote the initial draft. AJ and MH supervised the study. All authors approved the study.

## Conflict of interest

The authors declared there is no conflict of interest for this study.

## Ethical Permission

This study is mini review. All ethical principles were considered in this study.

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