Pharmacological Management of Bone Loss in Patients with Spondylodiscitis: A Systematic Review

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ABSTRACT

Introduction: Lytic bone defects are a common and devastating consequence of spondylodiscitis, often leading to vertebral collapse and spinal instability. Currently, there are no established guidelines for pharmacological management of this condition in conjunction with antibiotic therapy. **Objective:** To review the existing scientific evidence on the pharmacological treatment of bone loss secondary to spondylodiscitis. **Materials and Methods:** A systematic search was conducted in major medical databases to identify studies evaluating the use of teriparatide, romosozumab, or denosumab in patients with lytic bone defects associated with pyogenic spondylodiscitis or Pott's disease. **Results:** Two studies reported improved bone mineral density and enhanced osteoblastic activity following the use of teriparatide in patients with bone loss or osteoporosis associated with vertebral infection. Adverse reactions were minimal, and no interactions with antibiotic therapy were observed. In one of the studies, treatment was supplemented with romosozumab. A third study demonstrated improved outcomes in infected osteoblasts. Conversely, the use of bisphosphonates and denosumab was associated with poor outcomes and worsening of the infection. **Conclusions:** Anabolic agents such as teriparatide and romosozumab appear to be promising options for managing bone loss and severe osteoporosis in the context of vertebral infections, with a favorable safety profile. However, clinical trials are needed to confirm their efficacy.

Keywords: Discitis; spondylodiscitis; bone loss; tuberculosis; teriparatide; bisphosphonates; denosumab.

Level of Evidence: III

Manejo farmacológico de la pérdida ósea en pacientes con espondilodiscitis. Revisión sistemática

RESUMEN

Introducción: El defecto óseo lítico es una consecuencia devastadora y muy frecuente del paciente con espondilodiscitis, y es responsable del colapso y la inestabilidad. En la actualidad, no existe una pauta para el manejo farmacológico. **Objetivo:** Revisar la evidencia científica publicada sobre el tratamiento farmacológico de la perdida ósea secundaria a espondilodiscitis. **Materiales y Métodos:** Se realizó una búsqueda sistemática en bases de datos de referencia médica para hallar estudios sobre el uso de teriparatida, romosozumab o denosumab en pacientes con defecto lítico asociado a espondilodiscitis piógena, tuberculosis vertebral. **Resultados:** En dos artículos, se comunicó la mejoría de la densidad mineral y la formación osteoblástica con el uso de teriparatida en pacientes con defecto óseo u osteoporosis asociada a infección vertebral; las reacciones adversas fueron escasas, no hubo interacción con los antibióticos, y uno de ellos cuando se complementó con romosozumab. Un tercer artículo informó mejoría en los osteoblastos infectados. Asimismo, los bifosfonatos y el denosumab provocaron malos resultados y empeoraron la infección. **Conclusiones:** El uso de fármacos anabólicos, como teriparatida y romosozumab, promete ser una excelente opción para el tratamiento de la pérdida ósea y la osteoporosis severa en casos de infección vertebral, con escasas reacciones adversas. Se requieren estudios clínicos para verificarlo.

Palabras clave: Discitis; espondilodiscitis; pérdida ósea; tuberculosis; teriparatida; bifosfonatos; denosumab.

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INTRODUCTION

Spondylodiscitis is an infection affecting the intervertebral disc and adjacent vertebrae, which can result in significant bone loss and, secondarily, spinal instability.[1] Its incidence, although low (0.2–2.4/100,000 inhabitants in Western countries), has increased over the last 20 years due to prolonged life expectancy and a rise in comorbidities, leading to devastating consequences for patients, the healthcare system, and even mortality.[2]

Infectious involvement is associated with advanced osteolysis, vertebral destruction, instability, pain, severe disability, and, in some cases, serious neurological disorders.[3-5]

To date, various treatments have been implemented for spondylodiscitis, including bed rest, antibiotic therapy, and surgical intervention in cases of spinal instability or neurological compromise. However, no pharmacological treatment currently exists for vertebral destruction and bone defects.[6] Moreover, a significant number of patients with spinal infection also present with untreated subclinical osteoporosis—an association that has not yet been thoroughly studied.[2] Although the gold standard for diagnosing osteoporosis is bone mineral density measurement via DXA scanning, it is now possible to assess bone quality by quantifying Hounsfield units (HU) through computed tomography.[7-10]

Teriparatide, a parathyroid hormone analogue (PTH 1–34), is an anabolic agent that stimulates osteoblastic proliferation and currently plays a key role not only in the treatment of osteoporosis, but also in the prevention of complications and planning of spinal surgeries.[11-20] For this reason, it appears to be a promising agent in the management of bone defects associated with spinal infections.

The aim of this study was to review the current scientific evidence on the use of anabolic drugs and monoclonal antibodies in patients with spondylodiscitis, in order to determine whether they should be recommended for those presenting with bone loss or osteoporosis associated with the infection.

MATERIALS AND METHODS

This study was conducted in accordance with the PRISMA 2020 (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines.

Sources and Data Search

A systematic literature search in English was performed from January 2009 to March 2023 in the PubMed, Cochrane, LILACS, and SciELO databases using the MeSH terms: (((teriparatide) OR (romosozumab)) AND (((spine) OR (infection)) OR (spondylodiscitis))) AND ((bone defect) OR (bone loss))).

Filters were applied by year, text availability, article characteristics, article type, and publication date.

Inclusion Criteria

Analytical studies, randomized clinical trials, systematic reviews, narrative reviews, and case reports were included. The inclusion criteria comprised studies evaluating the use of teriparatide, romosozumab, or denosumab for treating bone defects associated with spinal infections in both human and animal models, as well as studies analyzing the relationship between osteoporosis and spondylodiscitis.

Exclusion criteria

Articles addressing osteoporosis or bone defects not associated with spondylodiscitis or involving vertebral tuberculosis were excluded. Also excluded were studies involving patients with osteoporosis secondary to other causes, such as chronic kidney disease, rheumatoid arthritis, and other metabolic, endocrine, or immunological conditions. Duplicates, unpublished studies, books, letters, and other documents were also discarded.

RESULTS

The initial search yielded 396 articles between 2009 and 2023 in PubMed, and 0 in Cochrane, SciELO, and LILACS. Continuing the selection process in PubMed, 375 articles were available in full text and written in English. Books, conference papers, abstracts, duplicate articles, unpublished studies, editorials, technical reports, and citations were excluded. This left a total of 207 studies. A second screening was conducted by reviewing the titles and abstracts. 199 studies were excluded for not being relevant to the research topic, as they included patients with osteoporosis secondary to endocrine, autoimmune, renal, or metabolic diseases, or patients receiving anabolic or antiresorptive drugs outside the context of vertebral infection.

Eight articles were identified that related osteomyelitis or spondylodiscitis to osteoporosis or bone loss. Of these, one was excluded because it did not address spondylodiscitis; another because it linked denosumab to infection risk in patients with low bone mineral density, but not with spondylodiscitis; a third because it was a review article on surgical site infection; and another because it focused solely on osteonecrosis management due to antiresorptive drugs and proinflammatory cytokines. Ultimately, four articles were selected for analysis: Two that associated anabolic agents with bone defects in patients with spondylodiscitis, one that evaluated the response of teriparatide to isoniazid and rifampicin, and one on the diagnosis of osteoporosis in patients with spondylodiscitis (Table).

Table. Selected articles meeting the inclusion criteria.

Author (Year)	Sample size	Objective	Dose/Interval	Germ	Interactions with antibiotics	Adverse events	Control		LE
							Imaging	Time	
Ohnishi et al. (2021)	1 patient	Literature review	Not specified	Not specified	None	Exanthem, surgical site infection	CT	3 wk, 6 wk, 2 m	III
Shinohara et al. (2014)	1 patient	To evaluate bone mineral density after teriparatide administration in patients with spondylodiscitis, bone destruction and a history of osteoporosis.	56.5 µg weekly, for 3 months	Not specified	None	Headache, nausea, vomiting	DXA	3 wk, 6 wk, 3 m	IV
Lee et al. (2022)	1 patient	To evaluate the use of teriparatide vs. antituberculosis drugs.	400 ng/ml, every 48 h, for 7 days	*M. tuberculosis*	None	None	No	1 wk, 4 wk	II

CT = computed tomography; DXA = bone density scan. LE = level of evidence.

Data Analysis

The review demonstrated that the available literature on this topic is limited. No randomized clinical trials or high-level evidence studies were identified.

The earliest study dates to 2014, in which Shinohara et al. administered 56.5 µg/week of teriparatide to a 78-year-old diabetic patient with spondylodiscitis and secondary bone destruction at T11. Bone mineral density (BMD) was assessed via DXA scan at 3, 6, and 12 weeks, showing a 17.6% increase in BMD as early as the third week, along with better resolution of the infection at 8 weeks. Reported adverse effects included nausea and headache. The authors recommended teriparatide administration in these patients.[6]

In 2020, Bettag et al. retrospectively analyzed 200 patients with spondylodiscitis treated surgically via posterior instrumentation and followed up for one year. Only 5% had a prior osteoporosis diagnosis and received pharmacological treatment. When bone density was assessed using Hounsfield units (HU) via computed tomography, 41% (81 patients) were found to have undiagnosed osteoporosis. Patients with HU <110 had a significantly higher rate of revision surgery and implant loosening. The authors recommended HU quantification in patients with spondylodiscitis and associated osteoporosis, and early initiation of anabolic treatment, such as teriparatide, due to the high risk of complications including fractures and implant loosening.[2]

In 2021, Ohnishi et al. administered teriparatide to a patient with spondylodiscitis, severe osteolysis, and an L3 fracture. Anabolic treatment was initiated but discontinued due to a rash. The patient subsequently underwent fixation from T12 to L5. A surgical site infection occurred 6 weeks after discontinuing teriparatide, accompanied by worsening osteolysis. Romosozumab was then initiated, resulting in a favorable response with bone bridging at 6 weeks and complete resolution of the infection.[1]

Finally, Lee et al. (2022) observed a 705% increase in alkaline phosphatase levels and osteoblastic activity at day 28 ($p < 0.0031$) after administering teriparatide at 400 ng/mL every 48 hours for 7 days, alongside isoniazid and rifampicin, against MG-63 cells infected with spinal tuberculosis. Infection was eradicated by day 7. There were no adverse reactions and no reduction in antibiotic efficacy.[21]

DISCUSSION

The bone defects and low mineral density associated with spinal infections pose a significant challenge for spinal surgeons due to irreparable structural loss, functional impairment, pain, and the frequent need for additional surgical interventions—all of which have a considerable economic impact.[1] The infectious process often leads to rapid and severe bone lysis and accelerated destruction.[22]

Molecular studies have shown that infection suppresses osteoblastogenesis and increases osteoclastic activity through the release of proinflammatory cytokines—such as tumor necrosis factor-alpha, interleukin-1β, and interleukin-6—by macrophages and lymphocytes. These cytokines bind to the receptor activator of nuclear factor kappa-B ligand (RANKL), which activates osteoclastogenesis via its receptor RANK.[23-28] Moreover, bone loss is further exacerbated by prolonged bed rest and lack of physical activity.[29]

Currently, there is no established consensus regarding the use of osteoanabolic drugs in the context of infection.[1] These agents have been used for managing osteoporosis in patients with osteomyelitis—not only in the spine, but also in other locations such as the femur and tibia—with the aim of preventing osteoclastic resorption and thereby minimizing structural damage.[30] Two major categories of bone-active drugs have been studied in the laboratory: anabolic agents (mainly teriparatide and romosozumab) and antiresorptives (bisphosphonates and denosumab).

Teriparatide, an analog of parathyroid hormone, exhibits anabolic effects by inhibiting osteoclast activity while simultaneously promoting bone formation—an advantage over antiresorptive agents, which inhibit resorption but also suppress osteogenesis and bone turnover.[1]

There is increasing evidence linking osteonecrosis of the jaw to infection as an early histological manifestation.[31,32] Various infections have been reported in association with antiresorptive therapy. Interestingly, teriparatide has emerged as the treatment of choice in such cases, owing to its bone-forming properties.[33,34] However, data on its use in patients with bone defects secondary to infection remain scarce, only a few case reports. However, there have been reports of its successful application in infected hip arthroplasty, septic arthritis of the elbow, and infected tibial nonunion—all without exacerbation of the infectious process.[35-37]

Romosozumab, a monoclonal antibody, inhibits sclerostin binding to low-density lipoprotein receptors (LRP-5 and LRP-6), leading to increased β-catenin levels in the osteoclast. This results in suppressed bone resorption and enhanced osteogenesis.[38]

Among antiresorptives, denosumab is a monoclonal antibody that inhibits the precursor of osteoclasts in mature cells by blocking RANKL. Although effective in managing osteoporosis,[39] several clinical trials have reported an increased incidence of infections such as cellulitis, erysipelas, surgical site infections, and urinary or gastrointestinal infections.[40,41] In a meta-analysis of 20,470 patients across 24 controlled trials, Catton et al. observed a statistically significant increase in the overall infection rate in patients treated with denosumab (relative risk: 1.11; 95% CI: 1.02–1.20; $p = 0.02$).[42] These findings suggest that denosumab may not be an ideal option for patients with spondylodiscitis, as it could potentially aggravate the infectious process. Further research is necessary to clarify this association.

Bisphosphonates, which are pyrophosphate analogs that bind to hydroxyapatite on the bone surface, are categorized into nitrogen-containing and non-nitrogen-containing types. The former are associated with osteoclast apoptosis and are more commonly used in the treatment of bone loss.[43] However, the nitrogen-containing molecule has also been found to enhance bacterial adhesion to the bone surface, potentially worsening infection. Additionally, they have been linked to inflammatory complications, including the development of osteomyelitis. As a result, bisphosphonates are not recommended in cases of vertebral osteomyelitis, as their potential to worsen infection outweighs their benefits in reducing bone resorption.[44,45]

The first line of management for spondylodiscitis is conservative treatment with antibiotics and analgesics. From the outset, the infection presents a lytic component that progresses to bone defects, vertebral destruction, and instability, with neurological repercussions in some patients.[1,6,21] In these cases, surgery offers the best alternative for management; however, it is often doomed to failure due to the progression of osteolysis and implant failure in patients who do not receive osteoforming therapy. This results in surgical reinterventions that pose life-threatening risks and are not favorable for the healthcare system.

For this reason, it is also recommended to quantify Hounsfield Units (HU) by computed tomography during spinal planning in order to reduce complications.[2]

Regarding adverse reactions, Shinohara et al. and Onishi et al., in their case series, recorded mild events such as rash, headache, nausea, and vomiting caused by anabolic agents. These were easily managed and did not interfere with antibiotic therapy, resolution of the infection, or the patients' overall health status. On the contrary, they observed signs of early bone formation around the third week.[1,6]

In addition to pyogenic spondylodiscitis, Lee et al. confirmed the osteoforming effect of teriparatide in a case of tuberculous spondylodiscitis with vertebral destruction, reporting no adverse reactions or drug-drug interactions.[21]

One of the most commonly used antibiotics in the treatment of spinal infections is vancomycin, which has demonstrated cytotoxic effects on osteoblasts.[46]

Tsuji et al. highlighted the protective effect of teriparatide after administering 7.5 µg over 24 hours to cultured bovine serum cells infected with spinal pathogens, successfully reducing vancomycin-induced cytotoxicity.[47]

The optimal dosage and administration interval of these anabolic agents have not yet been established. However, it is clear that treatment was initiated during the acute phase of infection, with signs of accelerated osteoformation observed within the first three weeks. This effect increased at six weeks and at three months in the reported cases,[1,6,21] and with a dose of 56 µg weekly in the study by Shinohara et al.[6]

Limitations of this study include the absence of controlled clinical trials to determine appropriate dosing and administration intervals for teriparatide and romosozumab; small patient sample sizes; insufficient evaluation of the cost-effectiveness of these agents; lack of standardized HU measurement by computed tomography in clinical practice; and the absence of a multidisciplinary approach integrating infectious disease and endocrinology specialists.

CONCLUSIONS

According to the limited available literature, teriparatide and romosozumab appear to be promising options in the management of bone defects and severe osteoporosis in patients with spondylodiscitis. They are associated with few adverse reactions and no drug-drug interactions. The use of antiresorptive agents is not recommended due to the potential risk of infection exacerbation.

Further clinical studies and stronger evidence are needed before these therapies can be routinely recommended in clinical practice.

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REFERENCES

1. Ohnishi T, Ogawa Y, Suda K, Komatsu M. Molecular targeted therapy for the bone loss secondary to pyogenic spondylodiscitis using medications for osteoporosis: A literature review. *Int J Mol Sci* 2021;22(9):4453. https://doi.org/10.3390/ijms22094453
2. Bettag C, Abboud T, von der Brelie C. Do we underdiagnose osteoporosis in patients with pyogenic spondylodiscitis? *Neurosurg Focus* 2020;49 (2):E16. https://doi.org/10.3171/2020.5.FOCUS20267

3. Yurube T, Han I, Sakai D. Concepts of regeneration for spinal diseases in 2021. *Int J Mol Sci* 2021;22(16):8356. https://doi.org/10.3390/ijms22168356
4. Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: an update. *Br Med Bull* 2016;117(1):121-38. https://doi.org/10.1093/bmb/ldw003
5. Pourtaheri S, Issa K, Stewart T, Shafa E, Ajiboye R, Buerba RA, et al. Comparison of instrumented and noninstrumented surgical treatment of severe vertebral osteomyelitis. *Orthopedics* 2016;39(3):e504-e508. https://doi.org/10.3928/01477447-20160427-07
6. Shinohara A, Ueno Y, Marumo K. Weekly teriparatide therapy rapidly accelerates bone healing in pyogenic spondylitis with severe osteoporosis. *Asian Spine J* 2014;8(4):498-501. https://doi.org/10.4184/asj.2014.8.4.498
7. Bazán PL, Cepeda R, Medina JR, Godoy A, Soria J, et al. Use of the hounsfield units in the spinal surgery planning. systematic review and meta-analysis. *Coluna/Columna* 2022;21(3):e264579. https://doi.org/10.1590/S1808-185120222103264579
8. St Jeor JD, Jackson TJ, Xiong AE, Freedman BA, Sebastian AS, Currier BL, et al. Average lumbar Hounsfield units predict osteoporosis-related complications following lumbar spine fusion. *Global Spine J* 2022;12(5):851-7. https://doi.org/10.1177/2192568220975365
9. Kim KJ, Kim DH, Lee JI, Choi BK, Han IH, Nam KH. Hounsfield units on lumbar computed tomography for predicting regional bone mineral density. *Open Med (Wars)* 2019;14:545-51. https://doi.org10.1515/med-2019-0061
10. Choi MK, Kim SM, Lim JK. Diagnostic efficacy of Hounsfield units in spine CT for the assessment of real bone mineral density of degenerative spine: correlation study between T-scores determined by DEXA scan and Hounsfield units from CT. *Acta Neurochir* 2016;158(7):1421-7. https://doi.org/10.1007/s00701-016-2821-5
11. Tsai SHL, Chien RS, Lichter K, Alharthy R, Alvi MA, Goya A, et al. Teriparatide and bisphosphonate use in osteoporotic spinal fusion patients: a systematic review and meta-analysis. *Arch Osteoporos* 2020;15(1):158. https://doi.org/10.1007/s11657020-00738-z
12. Bryant JP, Perez-Roman RJ, Burks SS, Wang MY. Antiresorptive and anabolic medications used in the perioperative period of patients with osteoporosis undergoing spine surgery: their impact on the biology of fusion and systematic review of the literature. *Neurosurg Focus* 2021;50(6):1-11. https://doi.org/10.3171/2021.3.FOCUS201049
13. Fatima N, Massaad E, Hadzipasic M, Shankar GM, Shin JH. Assessment of the efficacy of teriparatide treatment for osteoporosis on lumbar fusion surgery outcomes: a systematic review and meta-analysis. *Neurosurg Rev* 2021;44(3):1357-70. https//doi.org/10.1007/s10143-020-01359-3
14. Chaudhary N, Lee JS, Wu JY, Tharin S. Evidence for use of teriparatide in spinal fusion surgery in osteoporotic patients. *World Neurosurg* 2017;100:551-6. https://doi.org/10.1016/j.wneu.2016.11.135
15. Oba H, Takahashi J, Yokomichi H, Hasegawa T, Ebata S, Mukaiyama K, et al. Weekly teriparatide versus bisphosphonate for bone union during 6 months after multi-level lumbar interbody fusion for osteoporotic patients: A multicenter, prospective, randomized study. *Spine (Phila PA 1976)* 2020;45(13):863-71. https://doi.org/10.1097/BRS.0000000000003426
16. Ebata S, Takahashi J, Hasegawa T, Mukaiyama K, Isogai Y, Ohba T, et al. Role of weekly teriparatide administration in osseous union enhancement within six months after posterior or transforaminal lumbar interbody fusion for osteoporosis-associated lumbar degenerative disorders: A multicenter, prospective randomized study. *J Bone Joint Surg Am* 2017;99(5):365-72. https://doi.org/10.2106/JBJS.16.00230
17. Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Teriparatide accelerates lumbar posterolateral fusion in women with postmenopausal osteoporosis: prospective study. *Spine (Phila PA 1976)* 2012;37(23):E1464-8. https://doi.org/10.1097/BRS.0b013e31826ca2a8
18. Seki S, Hirano N, Kawaguchi Y, Nakano M, Yasuda T, Suzuki K, et al. Teriparatide versus low-dose bisphosphonates before and after surgery for adult spinal deformity in female Japanese patients with osteoporosis. *Eur Spine J* 2017;26(8):2121-7. https://doi.org/10.1007/s00586-017-4959-0
19. Kim JW, Park SW, Kim YB, Ko MJ. The effect of postoperative use of teriparatide reducing screw loosening in osteoporotic patients. *J Korean Neurosurg Soc* 2018;61(4):494-502. https://doi.org/10.3340/jkns.2017.0216
20. Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Comparison of teriparatide and bisphosphonate treatment to reduce pedicle screw loosening after lumbar spinal fusion surgery in postmenopausal women with osteoporosis from a bone quality perspective. *Spine (Phila PA 1976)* 2013;38(8):E487-92. https://doi.org/10.1097/BRS.0b013e31828826dd
21. Lee S, Seo YJ, Choi JY, Che X, Kim HJ, Eum SY, et al. Effect of teriparatide on drug treatment of tuberculous spondylitis: an experimental study. *Sci Rep* 2022;12(1):21667. https://doi.org/10.1038/s41598-022-25174-6

22. Shousha M, Boehm H. Surgical treatment of cervical spondylodiscitis: A review of 30 consecutive patients. *Spine (Phila PA)* 2012;37(1):E30-E36. https://doi.org/10.1097/brs.0b013e31821bfdb2
23. Yang J, Tang R, Yi J, Chen Y, Li X, Yu T, et al. Diallyl disulfifide alleviates inflammatory osteolysis by suppressing osteoclastogenesis via NF-κB-NFATc1 signal pathway. *FASEB J* 2019;33(6):7261-73. https://doi.org/10.1096/fj.201802172r
24. Komine M, Kukita A, Kukita T, Ogata Y, Hotokebuchi T, Kohashi O. Tumor necrosis factor-alpha cooperates with receptor activator of nuclear factor kappaB ligand in generation of osteoclasts in stromal cell-depleted rat bone marrow cell culture. *Bone* 2001;28(5):474-83. https://doi.org/10.1016/s8756-3282(01)00420-3
25. Kitaura H, Kimura K, Ishida M, Kohara H, Yoshimatsu M, Takano-Yamamoto T. Immunological reaction in TNF-α-mediated osteoclast formation and bone resorption in vitro and in vivo. *Clin Dev Immunol* 2013:2013:181849. https://doi.org/10.1155/2013/181849
26. Ruscitti P, Cipriani P, Carubbi F, Liakouli V, Zazzeroni F, di Benedetto P, et al. The role of IL-1β in the bone loss during rheumatic diseases. *Mediators Inflamm* 2015:2015:782382. https://doi.org/10.1155/2015/782382
27. Jules J, Zhang P, Ashley JW, Wei S, Shi Z, Liu J, et al. Molecular basis of requirement of receptor activator of nuclear factor κB signaling for interleukin 1-mediated osteoclastogenesis. *J Biol Chem* 2012;287(19):15728-38. https://doi.org/10.1074/jbc.m111.296228
28. Yoshitake F, Itoh S, Narita H, Ishihara K, Ebisu S. Interleukin-6 directly inhibits osteoclast differentiation by suppressing receptor activator of NF-kappaB signaling pathways. *J Biol Chem* 2008;283(17):11535-40. https://doi.org/10.1074/jbc.M607999200
29. Kim J, Jang SB, Kim SW, Oh JK, Kim TH. Clinical effect of early bisphosphonate treatment for pyogenic vertebral osteomyelitis with osteoporosis: An analysis by the Cox proportional hazard model. *Spine J* 2019;19(3):418-29. https://doi.org/10.1016/j.spinee.2018.08.014
30. Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature* 1999;397(6717):315-23. https://doi.org/10.1038/16852
31. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *J Bone Miner Res* 2015;30(1):3-23. https://doi.org/10.1002/jbmr.2405
32. Hoefert S, Schmitz I, Weichert F, Gaspar M, Eufifinger H. Macrophages and bisphosphonate-related osteonecrosis of the jaw (BRONJ): Evidence of local immunosuppression of macrophages in contrast to other infectious jaw diseases. *Clin Oral Investig* 2015;19(2):497-508. https://doi.org/10.1007/s00784-014-1273-7
33. Lee JJ, Cheng SJ, Jeng JH, Chiang CP, Lau HP, Kok SH. Successful treatment of advanced bisphosphonate-related osteonecrosis of the mandible with adjunctive teriparatide therapy. *Head Neck* 2011;33(9):1366-71. https://doi.org/10.1002/hed.21380
34. Lau AN, Adachi JD. Resolution of osteonecrosis of the jaw after teriparatide [recombinant human PTH-(1-34)] therapy. *J Rheumatol* 2009;36(8):1835-7. https://doi.org/10.3899/jrheum.081176
35. Mouyis M, Fitz-Clarence H, Manson J, Ciurtin C. Teriparatide: An unexpected adjunct for the treatment of a long-standing infected elbow prosthesis prevented arm amputation. *Clin Rheumatol* 2015;34(4):799-800. https://doi.org/10.1007/s10067-015-2909-y
36. Nishikawa M, Kaneshiro S, Takami K, Owaki H, Fuji T. Bone stock reconstruction for huge bone loss using allograft-bones, bone marrow, and teriparatide in an infected total knee arthroplasty. *J Clin Orthop Trauma* 2019;10(2):329-33. https://doi.org/10.1016/j.jcot.2018.03.004
37. Rollo G, Luceri F, Falzarano G, Salomone C, Bonura EM, Popkov D, et al. Effectiveness of teriparatide combined with the Ilizarov technique in septic tibial non-union. *Med Glas (Zenica)* 2021;18(1):287-92. https://doi.org/10.17392/1280-21
38. Chen Y, Alman A. Wnt pathway, an essential role in bone regeneration. *J Cell Biochem* 2009;106(3):353-62. https://doi.org/10.1002/jcb.22020
39. Ferrari-Lacraz S, Ferrari S. Do RANKL inhibitors (denosumab) affect inflammation and immunity? *Osteoporos Int* 2011;22(2):435-46. https//doi.org/10.1007/s00198-010-1326-y
40. Watts NB, Roux C, Modlin JF, Brown JP, Daniels A, Jackson S, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: Coincidence or causal association? *Osteoporos Int* 2012;23:327-37. https://doi.org/10.1007/s00198-011-1755-2
41. Toulis KA, Anastasilakis AD. Increased risk of serious infections in women with osteopenia or osteoporosis treated with denosumab. *Osteoporos Int* 2010;21:1963-4. https://doi.org/10.1007/s00198-009-1145-1

42. Catton B, Surangiwala S, Towheed T. Is denosumab associated with an increased risk for infection in patients with low bone mineral density? A systematic review and meta-analysis of randomized controlled trials. *Int J Rheum Dis* 2021;24(7):1-11. https://doi.org/10.1111/1756-185X.14101
43. Gong L, Altman RB, Klein TE. Bisphosphonates pathway. *Pharmacogenet Genom* 2011;21(1):50-3. https://doi.org/10.1097/fpc.0b013e328335729c
44. Ganguli A, Steward C, Butler SL, Philips GJ, Meikle ST, Lloyd AW, et al. Bacterial adhesion to bisphosphonate coated hydroxyapatite. *J Mater Sci Mater Med* 2005;16(4):283-7. https://doi.org/10.1007/s10856-005-0625-x
45. Thompson K, Freitag L, Styger U, Camenisch K, Zeiter S, Arens D, et al. Impact of low bone mass and antiresorptive therapy on antibiotic efficacy in a rat model of orthopedic device-related infection. *J Orthop Res* 2021;39(2):415-45. https://doi.org/10.1002/jor.24951.
46. Eder C, Schenk S, Trififinopoulos J, Külekci B, Kienzl M, Schildbsock S, et al. Does intrawound application of vancomycin influence bone healing in spinal surgery? *Eur Spine J* 2016;25(4):1021e8. https://doi.org/10.1007/s00586-015-3943-9
47. Tsuji KS, Kimura K, Tateda K, Takahashi H. Protective effect of teriparatide against vancomycin-induced cytotoxicity in osteoblasts. *J Orthop Sci* 2023;28(6):1384-91. https://doi.org/10.1016/j.jos.2022.09.018