



Mini Review

The effect of kyphoplasty and vertebroplasty on denosumab discontinuation rebound fractures

Paraskevas-Asimakis Velitsikakis^{1,2}, Stylianos Kopanos³, Georgios Giovanidis^{1,2}, Aikaterini Manta², Christos Zafeiris⁴

¹Postgraduate Program "Metabolic Bone Diseases", National and Kapodistrian University of Athens, Medical School, Athens, Greece;

²Orthopaedic Department, General Hospital of Chalkida, Chalkida, Greece;

³Fellow Researcher, Second Gynaecological and Obstetrics Department, Aretaieion Hospital, Athens, Greece;

⁴Laboratory for the Research of the Musculoskeletal System "Th. Garofalidis", National and Kapodistrian University of Athens, Medical School, Athens, Greece

Abstract

Denosumab is an antiresorptive agent that significantly reduces bone turnover markers, increases mineral density and as a result, decreases the risk of vertebral fractures. The drug holiday effect on denosumab is associated with a high risk of multiple vertebrae fractures soon after the withdrawal. Discontinuation reasons may vary, but common reasons are the patient's will, discontinuation due to an upcoming dental procedure and long treatment period. Treatment of these fractures can be either surgical augmentation or conservative with the use of antiresorptive drugs. The purpose of this scientific paper is to review current data on the effect of either kyphoplasty or vertebroplasty on these types of fractures. Several studies showed that surgical augmentation is associated with a higher risk of multiple vertebrae fractures in comparison with conservative treatment and thus, it is not recommended, though more research is needed.

Keywords: Kyphoplasty, Vertebroplasty, Denosumab, Rebound fractures

Introduction

Denosumab is a fully human monoclonal antibody, which inhibits the connection of the receptor activator of nuclear factor κB ligand to the RANK receptor. It is an antiresorptive agent which increases bone mineral density and reduces bone fracture risk^{1,2}.

The most common side effects of denosumab use in postmenopausal women are weakness bone, joint and muscle pain (more than 10%), constipation, rash, abdominal discomfort, sciatica and eczema (around 10%)³. The pivotal FREEDOM trial also revealed that denosumab use may cause osteonecrosis of the jaw and atypical femoral fractures, according to the FREEDOM trial in 13 out of 7600 patients and 3 out of 7600 patients, respectively. Patients who use denosumab should be closely monitored due to these potential adverse effects^{4,5}.

Drug holiday from denosumab is associated with multiple vertebral fractures for 6-8% of the patients who discontinue this treatment, according to the FREEDOM trial⁶⁻⁸. It has been recognized that the results of the discontinuation of

denosumab are quickly presented with a rapid decline in bone mineral density due to the increase of bone turnover markers^{9,10}. The regulation disorder of Wnt inhibitors, an excessive rise in the expression of RANKL and decreased levels of DKK-1 and SOST after the discontinuation of denosumab have been suggested to be the reason for the "rebound effect", though more research is needed¹¹⁻¹⁵. The case series report by Elisa Fernández Fernández et al (2018) showed that there is a significant change in the T-score in both Femoral Neck and Lumbar Spine. More

The authors have no conflict of interest.

Corresponding author: Paraskevas-Asimakis Velitsikakis, MD, Orthopaedic Department, General Hospital of Chalkida, Chalkida, Greece

E-mail: parisvelitsikakis@gmail.com

Edited by: Konstantinos Stathopoulos

Accepted 20 September 2022

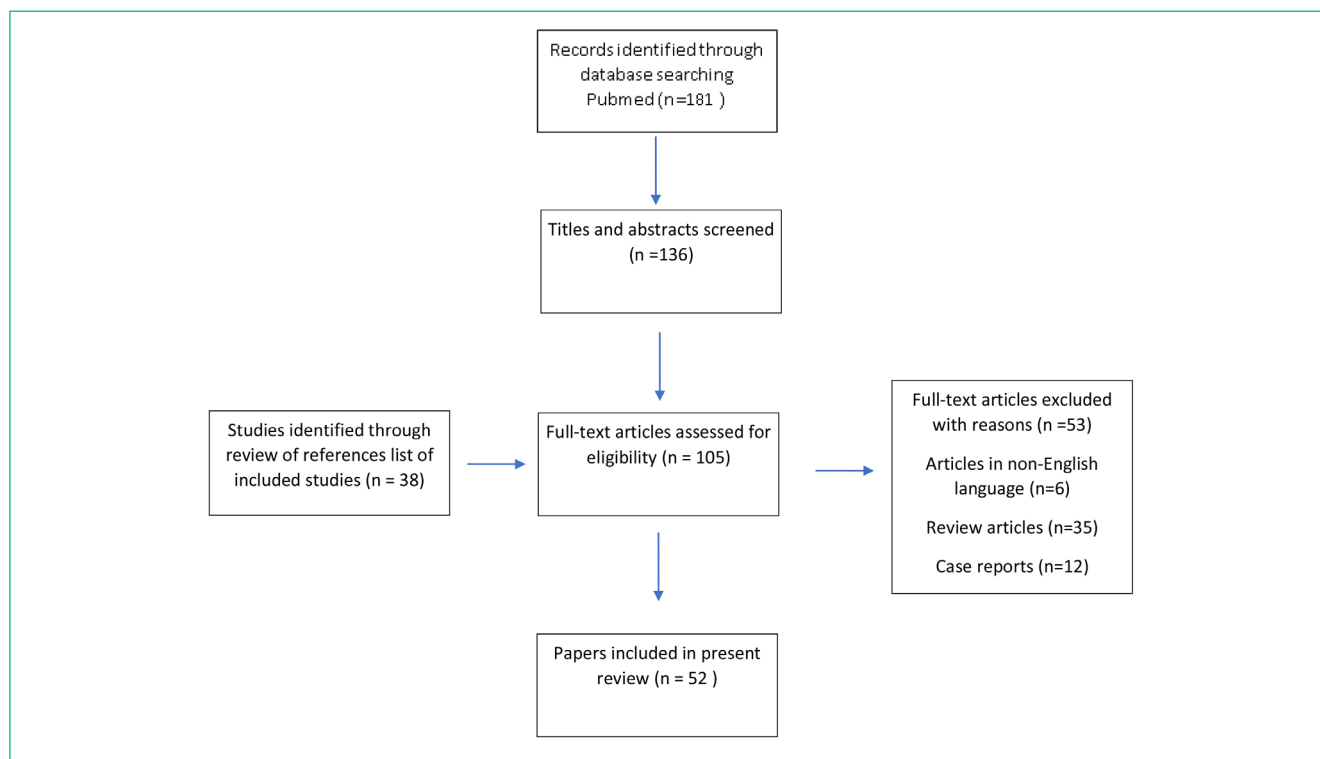


Table 1. Flowchart showing the selection strategy of the studies included in the mini systematic review.

specifically, the average T-score in the Femoral Neck (FN) during treatment was -2.6 ± 0.6 in the Femoral neck and -3.0 ± 1.3 in the Lumbar Spine (LS), but at least six months after the discontinuation of denosumab it was -3.2 ± 0.7 and -3.2 ± 1.6 respectively¹⁶. In the first year after denosumab discontinuation with no anti-resorptive substitute treatment, there is a 5-11% MBD loss rate¹⁷⁻²⁰. The most common reasons for discontinuation are treatment duration, low BMD ranges, cost coverage, concerns about long-term risks, dental procedures and patient's decision²¹.

Vertebral fractures can be minor or lead to pain, decreased physical function due to muscular or neurological deficiency, social isolation and depression, which together contribute to poorer quality of life. Quality of life is significantly lower in women with vertebral fractures, according to J.Saufelic-Genoves et al, measured with the Osteoporosis Quality of life Questionnaire²². Severe vertebrae fractures that cause back pain, reduced pulmonary function due to fractures of thoracic vertebrae and changes in mood, lead to an overall decline in quality of life²².

Withdrawal of denosumab has been correlated with a higher risk for major osteoporotic fractures and spontaneous multiple vertebral fractures^{23,24}. Multiple vertebral fractures are often symptomatic. The clinical manifestations include pain, functional impairment, height loss, kyphosis and scoliosis. It has been shown that the deformities of the

vertebral column shift the mechanical forces, and as a result, there is a higher risk for the occurrence of fragility vertebral fractures²⁵.

There are both conservative and surgical treatment modalities for vertebrae fractures. Unlike general types of vertebrae fractures, osteoporotic fractures are considered pathological fractures. Persistent pain due to instability is one of the most important reasons for surgical treatment. Vertebral augmentation, including vertebroplasty and kyphoplasty, is designed to stop pain from this type of fractures²⁶.

Materials and Methods

This is a simple literature review using the PubMed internet database. Papers were searched with the use of the following keywords: ("denosumab discontinuation") AND ("vertebral fracture" OR "drug holiday effect" OR "vertebroplasty" OR "kyphoplasty" OR "rebound fracture" OR "fracture"). Moreover, the reference lists of the included papers were scanned for additional studies. Prospective or retrospective evaluating the management of the rebound fractures of denosumab discontinuation were included in this review. Study protocols, case reports, systematic reviews, meta-analyses, studies in other than the English language, and non-human studies were excluded (Tables 1, 2).

Study	Number of patients	Number of patients that were treated with kypho/vertebroplasty	Number of patients that had new fracture after kyphoplasty/vertebroplasty	Time between -plasty and new fracture
Liana Tripto-Shkolnik et al (2021) ²⁷	12	2	0	Not Described
Elisa Fernández Fernández et al (2018) ¹⁶	10	2	2	Not Described
Voormolen MH et al (2006) ⁴⁷	66	66	26	12 (after 3 months) 5 (after 6 months) 3 (after 12 months)
Olivier Lamy et al (2017) ³⁰	9	3	3	In the month following the vertebroplasty
Anastasios D. Anastasilakis (2017) ²⁹	24	5	5	In the month following the vertebroplasty
Dupont et al (2019) ³⁴	4	2	2	2 months and 9 months respectively

Table 2. Summary of the reviewed case reports included in present scientific paper.

Results

Liana Tripto-Shkolnik et al in a case series (2021) report show that there is no consistent treatment for denosumab discontinuation rebound vertebral fractures. In this case report series, two patients were treated with surgical augmentation and both presented new multiple vertebrae fractures. The researchers conclude that kyphoplasty/vertebroplasty is not a recommendable treatment for this scenario²⁷.

Anastasilakis et al (2017) in a systemic review describe five cases of patients with denosumab withdrawal rebound fractures, that were subjected to vertebroplasty. All of these patients suffered new vertebral fractures months after the procedure. The authors of this review are suspecting that the bone strength is affected due to the cement that is infused, changing the forces that are applied to the intact vertebrae²⁸.

Surgical augmentation of denosumab discontinuation fractures due to severe pain was reported. All of these patients were treated with either percutaneous vertebroplasty or kyphoplasty and sustained new multiple vertebrae fractures²⁹⁻³¹. The American Academy of Orthopaedic Surgeons Clinical Practice Guideline strongly recommends against vertebroplasty for vertebral fracture related pain³². In contrast, patients treated with antiresorptive drugs did not present new vertebrae fractures during the evaluation period³³.

Dupont J. et al (2019) in a case series report, two patients underwent vertebroplasty and presented new multiple spontaneous vertebral fractures within twelve months of the procedure. Both patients started zoledronate after the procedure, which did not affect the avoidance of new fractures³⁴.

Conclusions

Vertebroplasty on denosumab discontinuation fractures of the vertebral column seems to increase the relative risk of new multiple vertebrae fractures for some patients³⁵. The reason why there are new fractures has not been clarified yet, but it has been suggested that the forces applied to the vertebrae change due to the infused orthopaedic cement^{28,29,36}. Many case series reports have shown that in a short post-operative period new vertebrae fractures do occur³⁷⁻⁴¹.

On the other hand, many patients that were treated with teriparatide, denosumab or other anti-resorptive agents, showed no new non-vertebral fractures, but some had new vertebrae fractures. The risk is lower in non-operative ways of treatment in comparison with vertebroplasty⁴²⁻⁴⁴. In the Denosumab Adherence Preference Satisfaction (DAPS) it has been shown that after the withdrawal of denosumab, other anti-resorptive agents do not protect entirely the patients from the rebound effect⁴⁵. Vertebroplasty as a treatment of osteoporotic vertebral fractures may be a risk factor for new cascade of vertebral fractures. The correlation between these fractures and vertebroplasty has not been confirmed due to many other factors that have a significant role and cannot be excluded, such as steroid consumption, osteoporosis, cement leakage into the disks and others⁴⁷⁻⁴⁹.

R.V. Chandra et al (2018) suggest in their systematic review that kyphoplasty and vertebroplasty do not increase the risk of new vertebral fractures in osteoporotic fractures not related to denosumab discontinuation⁵⁰. Current data shows that the risk of new vertebral fractures is not significantly increased by vertebral augmentation in comparison with conservative treatment within twelve months of the initial fracture⁵¹⁻⁵³.

References

- Pang KL, Low NY, Chin KY. A Review on the Role of Denosumab in Fracture Prevention. *Drug Des Devel Ther* 2020;14:4029-4051.
- Deeks ED. Denosumab: A Review in Postmenopausal Osteoporosis. *Drugs Aging* 2018;35(2):163-173.
- Amgen Europe B. V. Prolia 60 mg solution for injection in prefilled syringe: EU summary of product characteristics 2018.
- Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, Roux C, Törring O, Valter I, Wang AT, Brown JP. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *J Bone Miner Res* 2018;33(2):190-198.
- Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY, Roux C, Malouf J, Bradley MN, Daizadeh NS, Wang A, Dakin P, Pannacciulli N, Dempster DW, Papapoulos S. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017;5(7):513-523.
- Niimi R, Kono T, Nishihara A, Hasegawa M, Kono T, Sudo A. Rebound-associated vertebral fractures after discontinuation of denosumab for the treatment of maxillitis. *Osteoporos Int* 2018;29(3):769-772.
- Anastasilakis AD, Makras P, Yavropoulou MP, Tabacco G, Naci AM, Palermo A. Denosumab Discontinuation and the Rebound Phenomenon: A Narrative Review. *J Clin Med* 2021;10(1):152.
- Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporos Int* 2016;27(5):1929-30.
- Anastasilakis AD, Polyzos SA, Makras P, Trovas G, Yavropoulou MP, Tournis S. Efficacy of Antiosteoporotic Medications in Patients With Rebound-Associated Fractures After Denosumab Discontinuation. *J Clin Densitom* 2021;24(4):591-596.
- Lamy O, Stoll D, Aubry-Rozier B, Rodriguez EG. Stopping Denosumab. *Curr Osteoporos Rep* 2019;17(1):8-15.
- Anastasilakis AD, Evangelatos G, Makras P, Iliopoulos A. Rebound-associated vertebral fractures may occur in sequential time points following denosumab discontinuation: need for prompt treatment re-initiation. *Bone Rep* 2020;12:100267.
- Lyu H, Zhao SS, Yoshida K, Tedeschi SK, Xu C, Nigwekar SU, Leder BZ, Solomon DH. Delayed Denosumab Injections and Bone Mineral Density Response: An Electronic Health Record-based Study. *J Clin Endocrinol Metab* 2020;105(5):1435-44.
- McClung MR. Cancel the denosumab holiday. *Osteoporos Int* 2016;27(5):1677-1682.
- Tsourd E, Zillikens MC. Certainties and Uncertainties About Denosumab Discontinuation. *Calcif Tissue Int* 2018;103(1):1-4.
- Fassio A, Adami G, Benini C, et al. Changes in Dkk-1, sclerostin, and RANKL serum levels following discontinuation of long-term denosumab treatment in postmenopausal women. *Bone* 2019;123:191-195.
- Fernández Fernández E, Benavent Núñez D, Bonilla Hernán G, Monjo Henry I, García Carazo S, Bernad Pineda M, Balsa Criado A, Aguado Acín P. Multiple vertebral fractures following discontinuation of denosumab treatment: Ten clinical cases report. *Reumatol Clin (Engl Ed)* 2020;16(6):480-484.
- Zanchetta MB, Boailchuk J, Massari F, Silveira F, Bogado C, Zanchetta JR. Significant bone loss after stopping long-term denosumab treatment: a post FREEDOM study. *Osteoporos Int* 2018;29(1):41-47.
- Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* 2008;43(2):222-229.
- McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. *Osteoporos Int* 2017;28(5):1723-1732.
- Popp AW, Varathan N, Buffat H, Senn C, Perrelet R, Lippuner K. Bone Mineral Density Changes After 1 Year of Denosumab Discontinuation in Postmenopausal Women with Long-Term Denosumab Treatment for Osteoporosis. *Calcif Tissue Int* 2018;103(1):50-54.
- Noble JA, McKenna MJ, Crowley RK. Should denosumab treatment for osteoporosis be continued indefinitely? *Ther Adv Endocrinol Metab* 2021;12:20420188211010052.
- Sanfeliix-Genovés J, Hurtado I, Sanfeliix-Gimeno G, Reig-Molla B, Peiró S. Impact of osteoporosis and vertebral fractures on quality-of-life. a population-based study in Valencia, Spain (The FRAVO Study). *Health Qual Life Outcomes* 2011;9:20.
- Lyu H, Yoshida K, Zhao SS, et al. Delayed Denosumab Injections and Fracture Risk Among Patients With Osteoporosis: A Population-Based Cohort Study. *Ann Intern Med* 2020;173(7):516-526.
- Tripto-Shkolnik L, Fund N, Rouach V, Chodick G, Shalev V, Goldshtein I. Fracture incidence after denosumab discontinuation: Real-world data from a large healthcare provider. *Bone* 2020;130:115150.
- Sabo A, Hatgis J, Granville M, Jacobson RE. Multilevel Contiguous Osteoporotic Lumbar Compression Fractures: The Relationship of Scoliosis to the Development of Cascading Fractures. *Cureus* 2017;9(12):e1962.
- Balkarli H, Demirtas H, Kilic M, Ozturk I. Treatment of osteoporotic vertebral compression fractures with percutaneous vertebroplasty under local anesthesia: clinical and radiological results. *Int J Clin Exp Med* 2015;8(9):16287-16293.
- Tripto-Shkolnik L, Liel Y, Yekutieli N, Goldshtein I. Long-Term Follow-Up of Denosumab Discontinuers with Multiple Vertebral Fractures in the Real-World: A Case Series. *Horm Metab Res* 2021;53(3):185-190.
- Anastasilakis AD, Yavropoulou MP, Makras P. Bisphosphonates or denosumab discontinuation and risk of fractures. *Maturitas* 2017;102:75.
- Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. *J Bone Miner Res* 2017;32(6):1291-1296.
- Lamy O, Gonzalez-Rodriguez E, Stoll D, Hans D, Aubry-Rozier B. Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: 9 Clinical Cases Report. *J Clin Endocrinol Metab* 2017;102(2):354-358.
- Tripto-Shkolnik L, Rouach V, Marcus Y, Rotman-Pikielny P, Benbassat C, Vered I. Vertebral Fractures Following Denosumab Discontinuation in Patients with Prolonged Exposure to Bisphosphonates. *Calcif Tissue Int* 2018;103(1):44-49.
- Esses SI, McGuire R, Jenkins J, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the treatment of osteoporotic spinal compression fractures. *J Bone Joint Surg Am* 2011;93(20):1934-1936.
- Grassi G, Chiodini I, Palmieri S, Cairolì E, Arosio M, Eller-Vainicher C. Bisphosphonates after denosumab withdrawal reduce the vertebral fractures incidence. *Eur J Endocrinol* 2021;185(3):387-396.
- Dupont J, Laurent MR, Dedeigne L, Luyten FP, Gielen E, Dejaeger M. Rebound-associated vertebral fractures after stopping denosumab: Report of four cases. *Joint Bone Spine* 2020;87(2):171-173.
- Mattei TA, Mendel E, Bourekas EC. Vertebral compression fractures

- in patients under treatment with denosumab: a contraindication for percutaneous vertebroplasty? *Spine J* 2014;14(6):e29-35.
36. Tsourdi E, Zillikens MC, Meier C, Body JJ, Gonzalez Rodriguez E, Anastasilakis AD, Abrahamsen B, McCloskey E, Hofbauer LC, Guañabens N, Obermayer-Pietsch B, Ralston SH, Eastell R, Pepe J, Palermo A, Langdahl B. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab* 2020 Oct 26:dga756.
 37. Aubry-Rozier B, Gonzalez-Rodriguez E, Stoll D, Lamy O. Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports. *Osteoporos Int* 2016;27(5):1923-5.
 38. Florez H, Ramirez J, Monegal A, Guañabens N, Peris P. Spontaneous vertebral fractures after denosumab discontinuation: A case collection and review of the literature. *Semin Arthritis Rheum* 2019;49(2):197-203.
 39. Sosa-Henríquez M, Torregrosa O, Déniz A, Saavedra P, Ortego N, Turrión A, Pérez Castrillón JL, Díaz-Curiel M, Gómez-Alonso C, Martínez G, Antonio Blázquez J, Olmos-Martínez JM, Etxebarria Í, Caeiro JR, Mora-Peña D. Multiple vertebral fractures after suspension of denosumab. A series of 56 cases. *Int J Clin Pract* 2021;75(10):e14550.
 40. Tay WL, Tay D. Discontinuing Denosumab: Can It Be Done Safely? A Review of the Literature. *Endocrinol Metab (Seoul)* 2022;37(2):183-194.
 41. Burckhardt P, Faouzi M, Buclin T, Lamy O: The Swiss Denosumab Study Group. Fractures After Denosumab Discontinuation: A Retrospective Study of 797 Cases. *J Bone Miner Res* 2021;36(9):1717-1728.
 42. Anastasilakis AD, Trovas G, Balanika A, Polyzos SA, Makras P, Tournis S. Progression of Rebound-Associated Vertebral Fractures Following Denosumab Discontinuation Despite Reinstitution of Treatment: Suppressing Increased Bone Turnover May Not Be Enough. *J Clin Densitom* 2021;24(2):338-340.
 43. Anastasilakis AD, Tournis S, Yavropoulou MP, Polyzos SA, Makras P. Multiple Vertebral Fractures Following Denosumab Discontinuation: Are We Exaggerating? *Calcif Tissue Int* 2018;103(1):107-108.
 44. Kao FC, Hsu YC, Chen TS, Tu YK, Liu PH. Effects of Injected Antiosteoporotic Medication Versus Oral Bisphosphonates on Rates of Repeated Vertebroplasty or Kyphoplasty. *Clin Ther* 2020;42(6):1087-1098.e2.
 45. Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, Borenstein J, Kendler DL, DAPS Investigators (2012) Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int* 23(1):317-326.
 46. Che H, Breuil V, Cortet B, Paccou J, Thomas T, Chapuis L, Debais F, Mehseu-Cetre N, Javier RM, Loiseau Peres S, Roux C, Briot K. Vertebral fractures cascade: potential causes and risk factors. *Osteoporos Int* 2019;30(3):555-563.
 47. Ploeg WT, Veldhuizen AG, The B, Sietsma MS. Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: a systematic review. *Eur Spine J* 2006;15(12):1749-58.
 48. Voormolen MH, Lohle PN, Juttman JR, van der Graaf Y, Franssen H, Lampmann LE. The risk of new osteoporotic vertebral compression fractures in the year after percutaneous vertebroplasty. *J Vasc Interv Radiol* 2006;17(1):71-6.
 49. Chandra RV, Maingard J, Asadi H, Slater LA, Mazwi TL, Marcia S, Barr J, Hirsch JA. Vertebroplasty and Kyphoplasty for Osteoporotic Vertebral Fractures: What Are the Latest Data? *AJNR Am J Neuroradiol* 2018;39(5):798-806.
 50. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320-23
 51. Anderson PA, Froysheter AB, Tontz WL Jr. Meta-analysis of vertebral augmentation compared to conservative treatment for osteoporotic spinal fractures. *J Bone Miner Res* 2013;28:372-82.
 52. Shi MM, Cai XZ, Lin T, et al. . Is there really no benefit of vertebroplasty for osteoporotic vertebral fractures? A meta-analysis. *Clin Orthop Relat Res* 2012;470:2785-99.
 53. Cao J, Kong L, Meng F, et al. . Risk factors for new vertebral compression fractures after vertebroplasty: a meta-analysis. *ANZ J Surg* 2016;86:549-54.