ORIGINAL RESEARCH

Reducing Re-fractures Post Percutaneous Kyphoplasty: The Impact of Zoledronic Acid with Calcium and Vitamin D3 in Osteoporotic Patients

Weiqian Wu, MM; Wenbiao Zheng, MM; Weiwei Pan, MM; Fanghu Chen, MM; Langqing Jiang, MD

ABSTRACT

Background • Osteoporosis poses a significant health challenge characterized by reduced bone density and increased fracture risk. Percutaneous kyphoplasty, a common treatment, aims to stabilize vertebral fractures. However, adjunctive therapies like zoledronic acid remain underexplored in improving postoperative outcomes and bone health in these patients.

Objective • This study aims to evaluate the efficacy of zoledronic acid combined with calcium carbonate and vitamin D3 in treating osteoporosis, providing valuable clinical insights.

Methods • A cohort of sixty-six osteoporosis patients who underwent percutaneous kyphoplasty and received subsequent treatment at our hospital between March 2020 and March 2022 were selected. Thirty-three patients received calcium carbonate and vitamin D3 (control group), while the remaining thirty-three patients were treated with zoledronic acid alongside calcium carbonate and vitamin D3 (research group). Pre- and post-treatment assessments included bone mineral density measurements, bone metabolism and turnover marker evaluations, symptom improvement assessments using the Visual Analogue Scale (VAS) and the Oswestry Disability Index (ODI), monitoring of adverse reactions, and assessment of quality of life using the Core Quality of Life questionnaire (QOL-C30). A one-year follow-up was conducted to determine re-fracture incidence.

Results • Post-treatment, the research group exhibited significantly lower VAS, ODI, tartrate-resistant acid phosphatase-5b, and osteocalcin levels compared to the control group, while bone alkaline phosphatase levels were higher ($P < .05$). There was no significant difference in adverse reaction incidence between the groups ($P > .05$), but the research group demonstrated higher QOL-C30 scores ($P < .05$). Follow-up analysis revealed no notable difference in re-fracture rates between the groups ($P > .05$).

Conclusions • Zoledronic acid in combination with calcium carbonate and vitamin D3 effectively enhances bone health in osteoporosis patients, warranting its clinical recommendation. This regimen shows promise for improving patient outcomes in osteoporosis management. (*Altern Ther Health Med.* 2024;30(12):340-345).

Weiqian Wu, MM; **Wenbiao Zheng**, MM; **Weiwei Pan**, MM; **Fanghu Chen**, MM; **Langqing Jiang**, MD, Department of Orthopedics; Taizhou Municipal Hospital; Taizhou; Zhejiang; China.

Corresponding author: Langqing Jiang, MD
E-mail: jianglangqing@126.com

INTRODUCTION

Osteoporosis, primarily attributed to age-related factors, is characterized by diminished bone mass, microstructural deterioration, and heightened bone fragility, predisposing individuals to fractures.[1] This condition markedly affects the quality of life (QOL) in middle-aged and elderly individuals. Its prevalence increases with age, disproportionately affecting elderly women. Women over 60 have a prevalence rate nearly double that of men, reaching 50%.[2]

Osteoporosis patients face a significantly elevated risk of fractures and systemic metabolic bone diseases due to various factors such as bone mass loss, decreased bone density, microstructural deterioration, and increased bone fragility.[3] In China, the impact of osteoporosis is substantial, with approximately 2.33 million osteoporosis-induced fractures reported in 2010 alone. Moreover, projections suggest a continued increase in the number of affected individuals in the coming decades.[4,5]

Percutaneous kyphoplasty (PKP), considered the current gold standard clinical intervention for vertebral osteoporotic compression fractures accompanied by pain symptoms, offers pain relief through minimally invasive techniques, resulting in reduced trauma and accelerated postoperative recovery.[6] However, while PKP surgery effectively alleviates osteoporosis-related pain and enhances vertebral stability, it does not restore skeletal health.[7]

Re-fractures remain common among osteoporosis patients following PKP, primarily attributable to the continued decline in bone mineral density (BMD).[8] To support patient recovery and prevent subsequent fractures, individuals post-PKP should undergo anti-osteoporosis therapy.[9] Calcium carbonate and vitamin D3 represent commonly utilized treatments for osteoporosis, facilitating calcium absorption and supplementation while temporarily increasing bone mass; however, they have not yet demonstrated a curative effect.[10]

Zoledronic acid, a nitrogenous bisphosphonate compound, primarily targets human bones and inhibits bone resorption by suppressing osteoclast activity.[11] While some research has explored the combined use of these two drugs in treating osteoporotic fractures,[12] few studies have investigated their preventive effects on post-PKP refractures. Therefore, this study aims to examine the impact of zoledronic acid in combination with calcium carbonate and vitamin D3 on osteoporosis, providing insights and guidance for preventing refractures in osteoporosis patients following PKP treatment in the future.

DATA AND METHODS

Study Design

This study was a registered clinical randomized controlled trial. A total of 66 osteoporosis patients who had undergone PKP and relevant treatment at our institution between March 2020 and March 2022 were enrolled as research participants. These patients were randomly assigned into two groups using a randomized numerical table method: a research group (n=33) and a control group (n=33). The control group received calcium carbonate and vitamin D3 post-surgery, whereas the research group received zoledronic acid in combination with calcium carbonate and vitamin D3 post-surgery. The study was conducted in strict adherence to the principles outlined in the Declaration of Helsinki, with approval from the Ethics Committee of Taizhou Municipal Hospital.

Criteria for Patient Enrollment and Exclusion

Inclusion criteria were as follows: (1) All eligible patients met the diagnostic criteria for osteoporosis[13] and were diagnosed with thoracolumbar compression fractures through imaging examinations; (2) Patients met the indications for PKP and underwent the procedure at our hospital, with complete medical records and no cognitive or consciousness disorders; (3) Patients provided informed consent and agreed to participate in the study. Exclusion criteria were as follows: (1) Presence of malignancies or other significant medical conditions; (2) History of previous vertebral fractures or surgeries; (3) Abnormal liver and kidney function, immune system disorders, or coagulation dysfunction; (4) Contraindications to the medications used in the study; (5) Inability to comply with follow-up requirements.

Comparative Therapies in Osteoporosis Management

Both patient groups underwent PKP performed by the same surgical team at our hospital, followed by postoperative functional exercise. Patients in the control group received oral administration of calcium carbonate and vitamin D3 tablets (Wyeth Pharmaceutical Co., Ltd., SFDA Approval No. H10950029) following the surgery. Each patient took one tablet once or twice daily.

Pharmacological Intervention in the Research Group

Patients in the research group were administered zoledronic acid (Jiangsu Hengrui Pharmaceuticals Co., Ltd., SFDA Approval No. H20041953) in addition to the standard treatment received by the control group. Postoperatively, 4 mg of zoledronic acid was diluted in 100 ml of 0.9% sodium chloride injection or 5% glucose injection for intravenous infusion, with a drip duration of not less than 15 minutes.

Laboratory Analysis and Bone Density Measurement

Fasting elbow vein blood samples were collected from both patient groups upon admission to the hospital and after 2 weeks of treatment. After standing at room temperature for 30 minutes, the samples were centrifuged to obtain serum. Subsequently, tartrate-resistant acid phosphatase-5b (TRACP-5b), osteocalcin (OC), bone alkaline phosphatase (BAP), C-terminal telopeptide of type I collagen (CTX), procollagen type I N-terminal propeptide (PINP), and urinary type I collagen cross-linked N-telopeptide (NTX) levels were determined using an electrochemical analyzer (Myriad Automatic Chemiluminescent Immunoassay Analyzer, CL-9000i vet).

Bone Mineral Density (BMD) Measurements

Additionally, bone mineral density (BMD) measurements of the lumbar vertebrae L1~4 and femoral neck were performed using a BMD instrument (Nanjing Kejinshiye Co., Ltd, OSTEOKJ3000).

Prognostic Follow-up

Patients were followed up for one year, with scheduled reviews occurring at intervals of no more than 3 months between reexaminations.

Outcome Measures

Various assessment tools were utilized to evaluate treatment outcomes and patient well-being.

Assessment of Pain Severity Thoracolumbar Function. Pain severity was assessed using the Visual Analog Scale (VAS),[14] with higher scores indicating more severe pain symptoms. Utilized to quantify the intensity of pain experienced by patients before and after treatment, allowing for objective measurement of pain relief efficacy.

Assessment of Thoracolumbar Function. Additionally, changes in thoracolumbar function were measured using the Oswestry Disability Index (ODI),[15] with scores reflecting the extent of dysfunction. It assesses the impact of thoracolumbar dysfunction on daily activities, providing insights into functional improvements following treatment interventions.

Bone Health Parameters. BMD was measured to evaluate the effects of treatment on bone density, crucial for assessing osteoporosis management efficacy. Bone metabolism markers (TRACP-5b, OC, BAP)[16] were examined to monitor changes in bone turnover and metabolism, providing information on the bone remodeling process and treatment response.

Bone turnover markers C-terminal telopeptide of type I collagen (CTX), procollagen type I N-terminal propeptide (PINP), and urinary type I collagen cross-linked N-telopeptide (NTX) were also assessed before and after treatment. CTX was measured to assess bone resorption activity, providing insight into the rate of bone breakdown and turnover. PINP was examined to evaluate bone formation, reflecting the synthesis of new bone tissue and the efficacy of osteoblastic activity. NTX were analyzed to monitor bone resorption, offering information on the breakdown of collagen in bone tissue and overall bone turnover dynamics.

Incidence Adverse Reactions. We investigated the incidence of adverse reactions during treatment to assess the safety profile and tolerability of the therapeutic interventions. This analysis was crucial for identifying potential risks associated with the administered medications or procedures, and ensuring patient safety throughout the course of treatment.

Assessment of Quality of Life. To evaluate patients' quality of life (QOL) across physical, somatic, psychological, and social functioning dimensions, the Core Quality of Life questionnaire (QOL-C30) was administered. A higher score on the questionnaire indicates a better overall quality of life for patients undergoing treatment.

Incidence of Re-fractures. Additionally, the occurrence of re-fractures in both groups within one year after surgery was carefully recorded to assess the long-term effectiveness of the treatment interventions and the risk of recurrent fractures.

Statistical Analysis

Statistical analysis was conducted using SPSS version 23.0, with qualitative data represented as [n (%)] and compared using χ^2 tests. Quantitative data, described as mean ± standard deviation ($\bar{x} \pm s$), were analyzed between groups using *t*-tests and assessed for changes before and after treatment using paired *t* tests. Statistical significance was considered at $P < .05$.

RESULTS

Baseline Characteristics of Study Participants

Patient baseline data, comprising age, gender, and duration of osteoporosis, were collected upon admission. Comparison of these baseline characteristics revealed no significant inter-group differences ($P > .05$), refer to Table 1, suggesting comparability between the two study groups.

Pre- and Post-treatment Pain and Function Scores

Before treatment initiation, no significant difference was observed in the comparison of VAS and ODI scores between the two study groups ($P > .05$). After treatment, both VAS and ODI scores demonstrated a decrease in both groups. Importantly, post-treatment VAS and ODI scores were significantly lower in the research group compared to the control group ($P < .05$), refer to Figure 1, indicating superior symptom improvement in the research group.

Pre- and Post-treatment Bone Mineral Density (BMD)

Before treatment initiation, there was no significant difference in BMD between the two study groups ($P > .05$). After therapy, both groups exhibited an increase in BMD, with the research group demonstrating significantly higher BMD values at the lumbar vertebrae L1~4 and femoral neck compared to the control group ($P < .05$), refer to Figure 2.

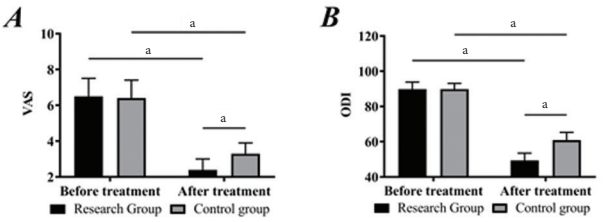
Table 1. Comparison of Baseline Information Between Both Groups [n (%)/ ($\bar{x} \pm s$)]

Group	Research	Control	χ^2/t	*P* value
Age	65.2±4.2	66.3±5.1	0.956	.342
Male / Female	14(42.4)/19(57.6)	15(45.5)/18(54.5)	0.062	.804
BMI (kg/m^2)	24.2±1.3	24.3±1.3	0.313	.756
Course of Osteoporosis (years)	3.5±1.3	3.3±1.2	0.649	.518
Combined High Blood Pressure			0.254	.614
Yes / No	21(63.6)/12(36.4)	19(57.6)/14(42.4)		
Combined Diabetes Mellitus			0.287	.592
Yes / No	22(66.7)/11(33.3)	24(72.7)/9(27.3)		

Note: The data are presented as mean±standard deviation ($\bar{x} \pm s$) or [n(%)].

Abbreviation: BMI, Body Mass Index.

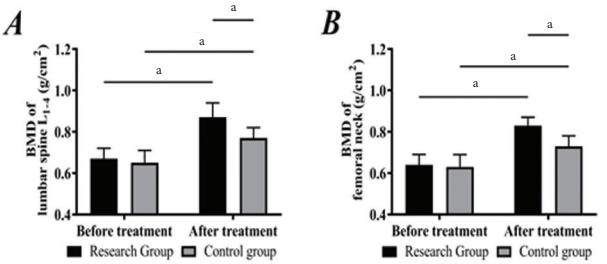
Figure 1. Comparison of Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI) Scores



[a]denotes statistical significance at $P < .05$.

Note: A and B represent the VAS and ODI scores before and after treatment for both patient groups, respectively.

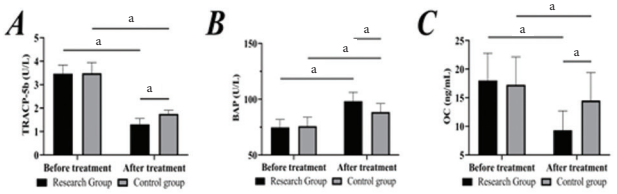
Figure 2. Comparison of Bone Mineral Density (BMD)



[a]denotes statistical significance at $P < .05$.

Note: Panels A and B display the BMD of the lumbar vertebrae L1 ~ 4 and femoral neck before and after treatment for both patient groups, respectively.

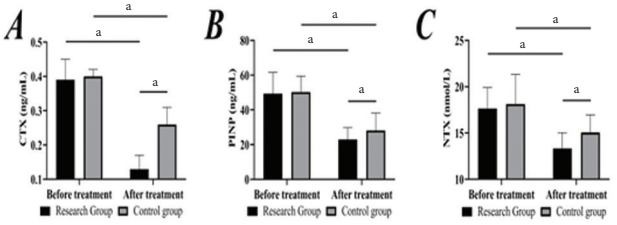
Figure 3. Comparison of Bone Metabolism



[a]denotes statistical significance at $P < .05$.

Note: Panels A, B, and C represent the levels of TRACP-5b, BAP, and OC before and after treatment for both patient groups, respectively.

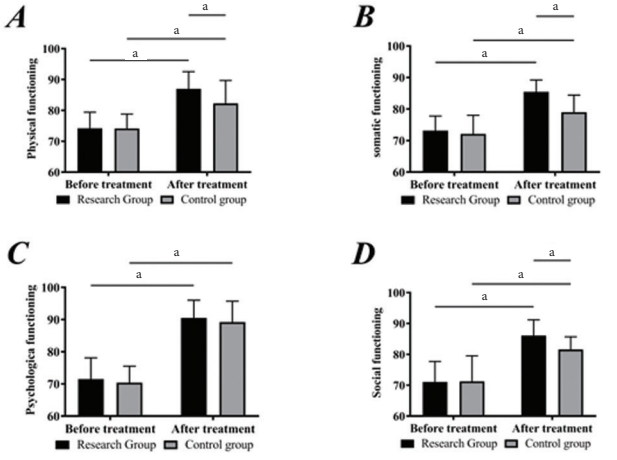
Figure 4. Comparison of Bone Turnover



[a]signifies statistical significance at $P < .05$.

Note: Panels A, B, and C depict the levels of CTX, PINP, and NTX before and after treatment for both patient groups, respectively.

Figure 5. Comparison of QOL Scores



"*" denotes statistical significance at $P < .05$.

Note: Panels A, B, C, and D represent the physical, somatic, psychological, and social functioning scores before and after treatment for both patient groups, respectively.

Table 2. Adverse Effects in Both Groups [n (%)]

Group	n	Nausea and Vomiting	Abdominal Pain and Diarrhea	Chills	Palpitations	Total Adverse Reaction Rate
Research	33	0(0)	1(3.0)	1(3.0)	0(0)	2(6.1)
Control	33	1(3.0)	1(3.0)	0(0)	1(3.0)	3(9.1)
χ^2						0.216
P value						0.642

Note: Data presented as [n (%)] unless otherwise indicated. A chi-square test (χ^2) was conducted to compare adverse reaction rates between groups. The *P*-value for comparison was .642, indicating no statistically significant difference in adverse reactions between the research and control groups.

Table 3. Re-Fracture within 1 Year after Surgery [n (%)]

Group	n	Re-Fracture	No Re-Fracture
Research	33	1(3.0)	32(97.0)
Control	33	5(15.2)	28(84.8)
$\chi 2$		2.933	
P value		.087	

Note: Data are presented as [n (%)]. χ^2 test was used for comparison between groups. $P < .05$ was considered statistically significant.

Pre- and Post-treatment Bone Metabolism

Following treatment, levels of TRACP-5b and OC decreased in both study groups, while BAP increased significantly ($P < .05$). However, the research group exhibited lower TRACP-5b and OC levels and higher BAP levels compared to the control group after treatment, indicating more effectively improved bone metabolism in the research group ($P < .05$), refer to Figure 3.

Pre- and Post-treatment Bone Turnover

Before treatment initiation, there were no significant inter-group differences observed in bone turnover markers, including CTX, PINP, and NTX ($P > .05$). However, post-treatment levels of these markers were significantly lower in the research group compared to the control group ($P < .05$). Notably, both study groups exhibited markedly reduced levels of bone turnover markers after treatment compared to baseline ($P < .05$), refer to Figure 4. The even lower values observed in the research group suggest a more pronounced improvement in bone turnover compared to the control group.

Pre- and Post-treatment Quality of Life (QOL) Scores

After treatment, both study groups exhibited increased QOL-30 scores compared to baseline ($P < .05$). While no significant difference was observed in the psychological domain scores between the two groups after treatment ($P > .05$), scores in the physical, somatic, and social domains were all significantly higher in the research group compared to the control group ($P < .05$), see Figure 5. These findings suggest a more pronounced improvement in overall quality of life in the research group following treatment.

Incidence of Adverse Reactions

Throughout the treatment period, occurrences of nausea and vomiting, abdominal pain and diarrhea, chills, and palpitations were reported in both study groups. Statistical analysis revealed no significant difference in the incidence of adverse reactions between the research and control groups ($P > .05$), refer to Table 2.

Re-fractures within 1 Year After Surgery

All subjects were successfully monitored during the 1-year prognostic follow-up period. Re-fractures were observed in 1 patient in the research group and 5 patients in the control group, with no significant inter-group difference in the incidence of re-fractures within one year after PKP ($P > .05$), see Table 3.

DISCUSSION

Both patient cohorts experienced significant reductions in post-treatment VAS and ODI scores. Notably, the research

group demonstrated even lower scores, suggesting that zoledronic acid combined with calcium carbonate and vitamin D3 offers a more pronounced advantage in alleviating pain and dysfunction in osteoporosis patients following PKP. These findings align with previous research results[17,18] and reaffirm the therapeutic benefits of this combination therapy for osteoporosis treatment.

The decline in BMD stands as the most significant and pivotal pathological alteration in the advancement of osteoporosis.[19] This decline is attributed, in part, to the continuous loss of bone mass resulting from age-related imbalances in bone remodeling and an elevated ratio of bone resorption to formation.[20] Furthermore, advancing age and declining estrogen levels contribute to the chronic inactivity of the immune system and perpetuate a state of pro-inflammatory response.

Inflammatory mediators such as IL-1 and TNF-α have been implicated in inducing the expression of receptor activator of nuclear factor κB (NF-κB) ligand, thereby stimulating osteoclasts and inhibiting osteoblasts, leading to osteopenia.[21,22] Consequently, monitoring changes in BMD during osteoporosis treatment becomes imperative.

In our study, we observed a notably higher BMD and more significant improvements in bone metabolism and turnover in the research group compared to the control group. These findings suggest that the combination therapy of zoledronic acid with calcium carbonate and vitamin D3 exhibits enhanced efficacy in promoting BMD recovery in osteoporosis patients. Zoledronic acid, known for its high affinity for mineralized bone, acts selectively on human bones.

By inhibiting farnesyl pyrophosphate synthase in osteoclasts, zoledronic acid effectively reduces bone resorption, leading to an increase in BMD).[23,24] This result aligns with the findings of Pavel et al.,[25] who observed a decline in bone turnover markers among elderly female osteoporosis patients following routine calcium and vitamin D supplementation, despite an increase in BMD. However, treatment with zoledronic acid sodium reversed these changes in bone turnover markers and significantly enhanced BMD levels.[25]

Our study corroborates these results, underscoring the valuable therapeutic role of zoledronic acid in combination with calcium carbonate and vitamin D3 for osteoporosis management. In an *in vitro* experiment conducted by Fizazi et al.,[26] it was observed that ZA enhanced the expression of the OPG gene in osteoblasts, aligning with our findings. However, since our study did not delve into the mechanism underlying this action, it remains plausible that there are additional pathways in action.

In comparing adverse reactions, it is evident that all patients experienced alleviation of symptoms after treatment, with no significant difference between groups. This finding suggests that zoledronic acid + calcium carbonate and vitamin D3 are safe and appropriate, even for elderly individuals with compromised immune systems. With such comprehensive intervention, we can anticipate further enhancement of quality of life in the research group, emphasizing the promising application of this treatment regimen for future osteoporosis management.

Surprisingly, we found no variance in re-fracture incidence between the groups, contrary to our expectations based on the superior bone health observed in the research group. This lack of statistical significance may stem from the limited sample size in both groups, leading to statistical analysis contingencies. To validate these findings, we intend to expand our research cohort promptly for a more comprehensive investigation.

Study Limitations

Despite the notable findings of our research, several limitations warrant consideration. Firstly, the relatively small sample size in our study may have influenced the statistical power and generalizability of our results. Additionally, the absence of a placebo-controlled group limits our ability to definitively attribute observed outcomes solely to the intervention. Moreover, the short-term follow-up duration may not capture potential long-term effects or complications associated with zoledronic acid + calcium carbonate and vitamin D3 treatment. Furthermore, the lack of exploration into the mechanistic pathways underlying treatment effects leaves unanswered questions regarding the precise biological mechanisms at play. Future studies with larger sample sizes, longer follow-up periods, and mechanistic investigations are essential to validate and expand upon our findings, ultimately advancing our understanding of osteoporosis management strategies.

Future Directions

In future investigations, it is imperative to expand the scope of analysis to encompass potential interactions between zoledronic acid + calcium carbonate and vitamin D3 treatment and common comorbidities in osteoporosis patients, such as diabetes and hypertension. Monitoring changes in basal blood sugar and blood pressure post-treatment will provide valuable insights into the safety profile of this therapeutic regimen. Furthermore, extending the duration of follow-up assessments will enable a thorough evaluation of long-term patient outcomes, shedding light on the sustained efficacy and safety of the treatment. Additionally, comparative studies with alternative osteoporosis treatment strategies will offer clinicians a comprehensive understanding of the relative benefits and drawbacks of different therapeutic approaches, facilitating informed decision-making in clinical practice.

CONCLUSION

In conclusion, our study demonstrates that zoledronic acid + calcium carbonate and vitamin D3 combination therapy shows promising results in the management of osteoporosis following percutaneous kyphoplasty. The treatment significantly alleviated pain, improved bone mineral density, enhanced bone metabolism, and positively impacted patients' quality of life. Despite the absence of a significant difference in

re-fracture rates between groups, the overall safety and efficacy profile of the intervention support its consideration as a viable treatment option for osteoporosis patients. Further research with larger sample sizes and longer follow-up periods is warranted to corroborate these findings and elucidate potential mechanisms underlying treatment efficacy.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. *Lancet*. 2022;399(10329):1080-1092. doi:10.1016/S0140-6736(21)02646-5
2. Johnston CB, Dagar M. Osteoporosis in Older Adults. *Med Clin North Am*. 2020;104(5):873-884. doi:10.1016/j.mcna.2020.06.004
3. Yong EL, Logan S. Menopausal osteoporosis: screening, prevention and treatment. *Singapore Med J*. 2021;62(4):159-166. doi:10.11622/smedj.2021036
4. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33(10):2049-2102. doi:10.1007/s00198-021-05900-y
5. Kendler DL, Cosman F, Stad RK, Ferrari S. Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review. *Adv Ther*. 2022;39(1):58-74. doi:10.1007/s12325-021-01936-y
6. Wang B, Zhao CP, Song LX, Zhu L. Balloon kyphoplasty versus percutaneous vertebroplasty for osteoporotic vertebral compression fracture: a meta-analysis and systematic review. *J Orthop Surg Res*. 2018;13(1):264. doi:10.1186/s13018-018-0952-5
7. Filippiadis DK, Marcia S, Masala S, Deschamps F, Kelekis A. Percutaneous Vertebroplasty and Kyphoplasty: Current Status, New Developments and Old Controversies. *Cardiovasc Intervent Radiol*. 2017;40(12):1815-1823. doi:10.1007/s00270-017-1779-x
8. Kyriakou C, Molloy S, Vrionis F, et al. The role of cement augmentation with percutaneous vertebroplasty and balloon kyphoplasty for the treatment of vertebral compression fractures in multiple myeloma: a consensus statement from the International Myeloma Working Group (IMWG). *Blood Cancer J*. 2019;9(3):27. doi:10.1038/s41408-019-0187-7
9. Zhang H, Xu C, Zhang T, Gao Z, Zhang T. Does Percutaneous Vertebroplasty or Balloon Kyphoplasty for Osteoporotic Vertebral Compression Fractures Increase the Incidence of New Vertebral Fractures? A Meta-Analysis. *Pain Physician*. 2017;20(1):E13-E28. doi:10.36076/ppj.2017.1.E13
10. Argyrou C, Karlafti E, Lampropoulou-Adamidou K, et al. Effect of calcium and vitamin D supplementation with and without collagen peptides on bone turnover in postmenopausal women with osteopenia. *J Musculoskelet Neuronal Interact*. 2020;20(1):12-17.
11. He B, Zhao JQ, Zhang MZ, Quan ZX. Zoledronic acid and fracture risk: a meta-analysis of 12 randomized controlled trials. *Eur Rev Med Pharmacol Sci*. 2021;25(3):1564-1573.
12. Jia F, Ruan L, Du C, et al. The nanoformula of zoledronic acid and calcium carbonate targets osteoclasts and reverses osteoporosis. *Biomaterials*. 2023;296:122059. doi:10.1016/j.biomaterials.2023.122059
13. Arceo-Mendoza RM, Camacho PM. Postmenopausal Osteoporosis: latest Guidelines. *Endocrinol Metab Clin North Am*. 2021;50(2):167-178. doi:10.1016/j.ecl.2021.03.009
14. Chiarotto A, Maxwell LJ, Ostelo RW, Boers M, Tugwell P, Terwee CB. Measurement Properties of Visual Analogue Scale, Numeric Rating Scale, and Pain Severity Subscale of the Brief Pain Inventory in Patients With Low Back Pain: A Systematic Review. *J Pain*. 2019;20(3):245-263. doi:10.1016/j.jpain.2018.07.009
15. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine*. 2000;25(22):2940-2952. doi:10.1097/00007632-200011150-00017
16. Delaney CP, Kiran RP, Senagore AJ, et al. Quality of life improves within 30 days of surgery for Crohn's disease. *J Am Coll Surg*. 2003;196(5):714-721. doi:10.1016/S1072-7515(03)00131-5
17. Quesada Gómez JM, Blanch Rubió J, Díaz Curiel M, Díez Pérez A. Calcium citrate and vitamin D in the treatment of osteoporosis. *Clin Drug Investig*. 2011;31(5):285-298. doi:10.1007/BF03256927
18. Ryhänen EM, Koski AM, Löyttyniemi E, Välimäki MJ, Kiviniemi U, Schalin-Jäntti C. Postoperative zoledronic acid for osteoporosis in primary hyperparathyroidism: a randomized placebo-controlled study. *Eur J Endocrinol*. 2021;185(4):515-524. doi:10.1530/EJE-21-0322
19. Migliorini F, Maffulli N, Colarossi G, Eschweiler J, Tingart M, Betsch M. Effect of drugs on bone mineral density in postmenopausal osteoporosis: a Bayesian network meta-analysis. *J Orthop Surg Res*. 2021;16(1):533. doi:10.1186/s13018-021-02678-x
20. Zeytinoglu M, Naaman SC, Dickens LT. Denosumab Discontinuation in Patients Treated for Low Bone Density and Osteoporosis. *Endocrinol Metab Clin North Am*. 2021;50(2):205-222. doi:10.1016/j.ecl.2021.03.004
21. Wu D, Cline-Smith A, Shashkova E, Perla A, Katyal A, Aurora R. T-Cell Mediated Inflammation in Postmenopausal Osteoporosis. *Front Immunol*. 2021;12:687551. doi:10.3389/fimmu.2021.687551
22. Livshits G, Kalinkovich A. Targeting chronic inflammation as a potential adjuvant therapy for osteoporosis. *Life Sci*. 2022;306:120847. doi:10.1016/j.lfs.2022.120847
23. Ward LM, Choudhury A, Alos N, et al. Zoledronic Acid vs Placebo in Pediatric Glucocorticoid-induced Osteoporosis: A Randomized, Double-blind, Phase 3 Trial. *J Clin Endocrinol Metab*. 2021;106(12):e5222-e5235. doi:10.1210/clinem/dgab458
24. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis. *Med Oral Patol Oral Cir Bucal*. 2020;25(3):e326-e336. doi:10.4317/medoral.23324
25. Pavel KP, Hubl W, Buchner M, Stadie G, Thiele HJ. [The development of a simple turbidimetric immunoprecipitation test for the determination of gentamicin in serum]. *Z Med Labdiagn*. 1988;29(6):348-353.
26. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813-822. doi:10.1016/S0140-6736(10)62344-6