Journal of Musculoskeletal and Neuronal Interactions JMNI

Cochrane Corner

Cochrane Rehabilitation
rehabilitation.cochrane.org

What are the treatment options for beta-thalassemia patients with osteoporosis? A Cochrane Review summary with commentary

Sina Arman

Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Keywords: Beta-thalassemia, Bisphosphonates, Osteoporosis, Treatment

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review "Treatment for osteoporosis in people with beta-thalassaemia"[1] by Bhardwaj et al.[a], published by Cochrane Cystic Fibrosis and Genetic Disorders Group. This Cochrane Corner is produced in agreement with the *Journal of Musculoskeletal and Neuronal Interactions* by Cochrane Rehabilitation with views* of the review summary author in the "implications for practice" section.

Background

Beta-thalassemia is a genetic condition characterized by reduced or absent synthesis of the beta-globin chains, which may increase the risk of osteoporosis in affected individuals[2-4]. Multiple factors contribute to the development of osteoporosis in beta-thalassemia patients, including bone marrow expansion, iron overload, endocrine complications (primarily hypogonadism), chronic liver disease, renal dysfunction, use of iron chelators, inadequate nutrition (deficiencies in vitamin D and zinc), related genetic factors (COL1A polymorphism), and reduced physical activity[2,3,5-8]. These factors disrupt bone remodeling by suppressing osteoblast function and increasing osteoclast activity, resulting in increased bone turnover, reduced trabecular bone tissue, cortical thinning, and decreased bone mineral density (BMD), ultimately leading to an increased risk of osteoporotic fractures[2,5,9].

Optimizing bone health and preventing or treating osteoporosis in this condition requires a multifaceted approach that includes careful management of beta-thalassemia (optimized blood transfusion, sufficient iron chelation, etc.), healthy nutrition (adequate intake of calcium, zinc, and vitamin D), regular exercise, hormonal replacement therapy, and pharmacological agents[2,3,5,8].

Although several randomized controlled trials (RCTs) have investigated the efficacy and safety of anti-osteoporosis drugs, more evidence-based data is needed to determine the most effective available treatment for beta-thalassemia-associated osteoporosis[1,3]. This Cochrane Review[1] aims to identify evidence on the efficacy and safety of treatment options for osteoporosis in patients affected by beta-thalassemia.

The author declares no conflicts of interest.

Corresponding author: Sina Arman, Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
E-mail: sinabox@gmail.com

[a] This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD010429. DOI: 10.1002/14651858.CD010429.pub3. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges, and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

* The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

Treatment for osteoporosis in people with beta-thalassaemia

(Amit Bhardwaj, Kye Mon Min Swe, Nirmal K. Sinha, 2023)[1]

What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to investigate the efficacy and safety of treatments for osteoporosis in patients with beta-thalassemia.

What was studied in the Cochrane Review?

This review included patients with a BMD Z-score of less than -2 among children under the age of 15, adult males aged 15 to 50 years, and premenopausal females over the age of 15 who had been diagnosed with beta-thalassemia. It also included postmenopausal women and men over the age of 50 who had a BMD T-score of less than -2.5 and were diagnosed with beta-thalassemia.

The interventions studied included a range of treatments for osteoporosis, such as bisphosphonates, hormone replacement therapy, calcitonin, blood transfusion (to reduce bone marrow expansion), hydroxyurea (to decrease the necessity for blood transfusions and subsequently reduce complications associated with chronic transfusion therapy), zinc (which plays a crucial role in bone metabolism), denosumab, and strontium ranelate, among others.

The interventions studied included various treatments for osteoporosis such as bisphosphonates, hormone replacement therapy, calcitonin, blood transfusion (reduce bone marrow expansion), hydroxyurea (reduce the need for blood transfusions and consequently decrease complications associated with chronic transfusion therapy), zinc (to increase bone mass and linear growth), denosumab, and strontium ranelate, among others[1]. The eligible controls consisted of a placebo, no treatment, or another intervention. Furthermore, controls could also include the same intervention with a different dosing regimen, adjuvant therapy, or a combination of the two. The primary outcome of the review was the absolute or percentage change in BMD Z-score, as measured by dual X-ray absorptiometry or computerized tomography, at specific regions of interest (total hip or femoral neck, spine, and wrist), as well as the incidence of clinical or radiographic fractures. The secondary outcomes included participant-reported mobility, quality of life as reported in the individual trials, treatment-related adverse effects such as upper gastrointestinal symptoms reported by participants, and bone pain, including its intensity, frequency, and duration.

Search methodology and up-to-dateness of the Cochrane Review?

The authors of the review conducted a search in the Haemoglobinopathies Trials Register of the Cochrane Cystic Fibrosis and Genetic Disorders Group. This register contains references that were found through comprehensive electronic database searches and manual searches of relevant journals and abstract books from conference proceedings. The search was conducted until August 4, 2022. Additionally, the authors also searched online trial registries without any limitations on language or publication status.

What are the main results of the Cochrane Review?

The Cochrane Review included six RCTs with a total of 298 participants. These trials consisted of three trials with 169 participants who received bisphosphonates, one trial with 42 participants who received zinc supplementation, one trial with 63 participants who received denosumab, and one trial with 24 participants who received strontium ranelate. The certainty of the evidence ranged from moderate to very low in these studies due to the small number of participants and potential bias related to randomization, allocation concealment, and blinding. The findings from these trials were as follows:

Bisphosphonates versus placebo or no treatment (two trials)

In one study involving 25 participants, it was found that alendronate and clodronate may increase the BMD Z-score at the femoral neck (mean difference (MD) 0.40, 95% confidence interval (CI) 0.22 to 0.58) and at the lumbar spine (MD 0.14, 95% CI 0.05 to 0.23) compared to placebo over a two-year period. Another study with 118 participants observed that neridronate may increase BMD at the lumbar spine, hip, and femoral neck after six and twelve months of treatment compared to no treatment. However, neridronate only increased BMD at the femoral neck compared to no treatment after 12 months. There was very low certainty in all of the results. No adverse effects were reported. Despite the low certainty of the evidence, the authors of the review considered the fact that participants receiving neridronate reported less back pain as an indicator of improved quality of life. One participant in the neridronate trial (116 participants) sustained multiple fractures due to a traffic accident. None of the trials reported wrist BMD or mobility.

Different doses of bisphosphonate compared (one trial)

Based on a 12-month trial involving 26 participants, the effects of different doses of pamidronate (60 mg versus 30 mg) were evaluated. The study found that the 60 mg dose had a higher BMD Z-score at the spine (MD 0.43, 95% CI 0.10 to 0.76) and forearm (MD 0.87, 95% CI 0.23 to 1.51) compared to the 30 mg dose. However, there was no significant difference at the femoral neck (very low-certainty evidence). Fracture incidence, mobility, quality of life, and adverse effects of treatment were not reported in this trial.

Zinc versus placebo (one trial)

A trial involving 42 participants showed that zinc supplementation likely increased BMD Z-scores at the lumbar spine after 12 months (MD 0.15, 95% CI 0.10 to 0.20; 37 participants) and 18 months (MD 0.34, 95% CI 0.28 to 0.40;

32 participants). A similar pattern was observed for BMD at the hip after 12 months (MD 0.15, 95% CI 0.11 to 0.19; 37 participants) and 18 months (MD 0.26, 95% CI 0.21 to 0.31; 32 participants). There was moderate certainty in the evidence for these results. However, no information was reported regarding the BMD of the wrist, fracture incidence, mobility, quality of life, or adverse effects of the treatment in the trial.

Denosumab versus placebo (one trial)

The authors were unsure about the impact of denosumab on BMD Z-scores at the lumbar spine, femoral neck, and wrist joint after 12 months when compared to placebo (low-certainty evidence). This conclusion was based on one trial involving 63 participants. Fracture incidence, mobility, quality of life, and adverse effects of treatment were not reported in this trial. However, the investigators reported a decrease in bone pain measured by visual analogue scale in the denosumab group after 12 months of treatment compared to placebo (MD -2.40 cm, 95% CI -3.80 to -1.00).

Strontium ranelate (one trial)

Only one trial consisting of 24 participants reported an increase in BMD Z-score at the lumbar spine in the intervention group, with no change observed in the control group (very low certainty evidence). In addition, the group that received strontium ranelate experienced a decrease in back pain compared to the placebo group (MD -0.70 cm, 95% CI -1.30 to -0.10). The authors consider this to be an improvement in the participants' quality of life.

What did the authors conclude?

The authors of the review concluded that after two years of treatment, bisphosphonates may increase BMD at the femoral neck, lumbar spine, and forearm compared to placebo. Moreover, they found that after 12 months, zinc supplementation probably increases BMD at the lumbar spine and hip. It is unclear whether denosumab has a significant effect on BMD, and the impact of strontium on BMD remains uncertain. The authors recommend further long-term RCTs on different bisphosphonates and zinc supplementation therapies for individuals with beta-thalassemia-associated osteoporosis.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Beta-thalassemia is a challenging clinical condition that requires lifelong, multidisciplinary care[5]. The treatment of comorbidities, in addition to blood transfusions and iron chelation therapy, has become crucial in effectively managing beta-thalassemia due to the increased life expectancy of patients[9,10].

Osteoporosis and osteoporotic fractures continue to cause significant morbidity among thalassemia patients, even when they receive adequate transfusions, chelation, and hormone replacement therapy. To prevent fractures, disability, and a decline in quality of life associated with thalassemia-related osteoporosis, general measures and lifestyle changes are necessary, along with physical activity and exercise, calcium and vitamin D supplements, and prescribing specific medications[2,3,5,8,11-13]. Therefore, rehabilitation professionals must be knowledgeable about the prevention, early diagnosis, and effective treatment of osteoporosis in these patients.

Regarding the pharmacological management of osteoporosis, this review suggests that bisphosphonates (with very low certainty evidence), zinc supplements (with moderate certainty evidence), and probably strontium ranelate (with very low certainty evidence) could be used to treat osteoporosis in patients with beta-thalassemia[1]. Some of these review findings align with the recommendations made by the Thalassemia International Federation (TIF) about the use of bisphosphonates and other novel treatment options[3]. Based on data from numerous RCTs or meta-analyses, the TIF recommends administering bisphosphonates along with calcium and vitamin D supplementation for a maximum of two years. They also suggest that intravenous administration of pamidronate or zoledronic acid may be more effective than oral bisphosphonates. Additionally, the TIF states that the potential impact of novel agents such as denosumab and teriparatide in the treatment of thalassemia-associated osteoporosis is currently under investigation, but their efficacy in thalassemia-associated osteoporosis has not yet been proven[3].

According to these results and suggestions, it is important to note that well-designed RCTs with long-term follow-up are still necessary to determine the efficacy and safety of different bisphosphonates, other pharmacological agents, and supplementation therapies for the treatment of osteoporosis in patients with beta-thalassemia.

Disclosures

There are no conflicts of interest declared by the author.

Acknowledgements

The author thanks Cochrane Rehabilitation and Dr. Silvia Minozzi for reviewing the contents of the Cochrane Corner.

References

1. Bhardwaj A, Swe KM, Sinha NK, Osunkwo I. Treatment for osteoporosis in people with ß-thalassaemia. Cochrane Database Syst Rev 2023;5:CD010429.
2. Gagliardi I, Celico M, Gamberini MR, Pontrelli M, Fortini M, Carnevale A, et al. Efficacy and safety of teriparatide in beta-thalassemia major Associated osteoporosis: a real-life experience. Calcif Tissue Int 2022;111(1):56-65.
3. Farmakis D, Porter J, Taher A, Cappellini MD, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the management of transfusion-dependent thalassemia. Hemasphere

2022;6(8):e732.
4. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. N Engl J Med 2021;384(8):727-743.
5. Giusti A, Pinto V, Forni GL, Pilotto A. Management of beta-thalassemia-associated osteoporosis. Ann N Y Acad Sci 2016;1368(1):73-81.
6. Yavropoulou MP, Anastasilakis AD, Tzoulis P, Tournis S, Rigatou E, Kassi E, et al. Approach to the management of β thalassemia major associated osteoporosis - A long-standing relationship revisited. Acta Biomed 2022;93(5):e2022305.
7. Piriyakhuntorn P, Tantiworawit A, Phimphilai M, Srichairatanakool S, Teeyasoontranon W, Rattanathammethee T, et al. The efficacy of alendronate for the treatment of thalassemia-associated osteoporosis: a randomized controlled trial. Front Endocrinol (Lausanne) 2023;14:1178761.
8. De Sanctis V, Soliman AT, Elsefdy H, Soliman N, Bedair E, Fiscina B, et al. Bone disease in β thalassemia patients: past, present and future perspectives. Metabolism 2018;80:66-79.
9. Gaudio A, Morabito N, Catalano A, Rapisarda R, Xourafa A, Lasco A. Pathogenesis of thalassemia major-associated osteoporosis: a review with insights from clinical experience. J Clin Res Pediatr Endocrinol 2019;11(2):110-117.
10. Giusti A. Bisphosphonates in the management of thalassemia-associated osteoporosis: a systematic review of randomised controlled trials. J Bone Miner Metab 2014;32(6):606-615.
11. Venou TM, Barmpageorgopoulou F, Peppa M, Vlachaki E. Endocrinopathies in beta thalassemia: a narrative review. Hormones (Athens) 2023 Dec 16. Epub ahead of print.
12. Morabito N, Catalano A, Gaudio A, Morini E, Bruno LM, Basile G, et al. Effects of strontium ranelate on bone mass and bone turnover in women with thalassemia major-related osteoporosis. J Bone Miner Metab 2016;34(5):540-546.
13. Thavonlun S, Houngngam N, Kingpetch K, Numkarunarunrote N, Santisitthanon P, Buranasupkajorn P, et al. Association of osteoporosis and sarcopenia with fracture risk in transfusion-dependent thalassemia. Sci Rep 2023;13(1):16413.