World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Impact of Bisphosphonate Discontinuation on Bone Density, Turnover, and Fracture Risk in Children With Osteogenesis Imperfecta: A Literature Review

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World Journal of Advanced Research and Reviews, 2025, 28(02), 2524-2531

Publication history: Received on 18 October 2025; revised on 24 November 2025; accepted on 27 November 2025

Article DOI: https://doi.org/10.30574/wjarr.2025.28.2.3972

Abstract

Bisphosphonate therapy is effective at increasing Bone Mineral Density (BMD) and decreasing fractures in children with Osteogenesis Imperfecta (OI), but long-term use has the potential to cause bone remodeling oversuppression. Drug holidays are proposed as a strategy to balance these benefits and risks. This study aimed to analyze the safety and efficacy of drugs holidays in children with OI through literature review conducted systematically on PubMed, Scopus, and Science Direct for publications in 2000-2025. Of the 423 articles identified, 9 studies met the inclusion criteria and were analyzed based on changes in BMD, Bone Turnover Markers (BTM), as well as fracture incidence. The majority of studies show that drug holidays do not increase the incidence of fractures and are able to maintain BMD, especially in children approaching the end of growth. However, a small percentage of studies report a decrease in BMD or an increase in BTM in patients who are still in the active growth phase. Overall, a drug holiday can be a safe strategy in patients with well-reacted therapies and a steady increase in BMD, with regular monitoring to determine retreatment needs and ensure long-term safety.

Keywords: Osteogenesis Imperfecta; Bisphosphonates; Drug Holiday; Bone Mineral Density; Bone Turnover Markers; Fracture Incidence

1. Introduction

Osteogenesis Imperfecta (OI) is a rare congenital disorder due to a genetic mutation in the type I collagen gene that is the main constituent of the Extracellular Matrix (ECM) (1,2). As a result, there is a disruption in the formation of the bone matrix, so that the bones become brittle and easily broken even with mild trauma (3). This condition is characterized by a variety of clinical manifestations depending on the type of OI, such as bone deformity, recurrent fractures, growth disorders, sclera discoloration, and hearing loss (4). OI therapeutic approaches require multidisciplinary management to achieve optimal therapeutic outcomes, including pharmacological and non-pharmacological therapies (5).

Bisphosphonate therapy is one of the main pharmacological treatments used widely in OI patients. Bisphosphonates are anti-resorptive that directly inhibit the activity of osteoclasts and have a high affinity for the mineral matrix in bone tissue, resulting in bisphosphonates accumulating in bone for a long time, about 1 to 10 years (6,7). However, bisphosphonate administration is cyclic and long-term, so the effectiveness and optimal duration of administration still need to be reviewed (8). The accumulation of drugs in bone tissue due to long-term use can affect the bone remodeling process and increase the risk of specific side effects (8,9).

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Long-term studies show that bisphosphonate therapy in children with OI is effective in increasing Bone Mineral Density (BMD), lowering the risk of fractures and Bone Turnover Markers (BTM) (10). Response to therapy may vary depending on the type of OI and the duration of treatment. Children with more severe type OI (OI type III/IV) tend to require longer therapy to achieve significant increases in BMD compared to the milder type (OI type I) (11). One study suggests that after the final high, the additional benefits of bisphosphonate for increasing bone mass may no longer be significant (12). Although effective, long-term use of bisphosphonates can cause bone remodeling oversuppression, which is a condition when osteoclast activity is suppressed excessively so that the cycle of bone turnover is disrupted and there is an accumulation of microfractures and micronecrosis that cannot be resorbed by *osteoclasts* (Ikebe 2013; Mandal et al. 2025). Complications due to this mechanism can be found in the Atypical Femoral Fracture (AFF), Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) (13,14).

The concept of drug holiday is the temporary cessation of bisphosphonate therapy after a long-term period in a child with Osteogenesis Imperfecta (OI), this strategy aims to balance between the benefits of bisphosphonate therapy and the potential risk of side effects due to long-term use. However, there is no clear international consensus on drug holiday in OI patients (11,15). Therefore, the study was prepared using literature review methods to analyze the effectiveness of drug holidays on long-term therapy of children with OI. The results of this study are expected to provide a more comprehensive understanding of the effectiveness of the duration of therapy, the potential application of drug holidays, and the direction of developing safer and effective therapeutic policies for OI patients in the future.

2. Material and Methods

This study is a literature review that aims to review the potential of drug holiday on long-term bisphosphonate therapy in children with Osteogenesis Imperfecta (OI). The literature search was conducted systematically through the PubMed, Scopus, and Science Direct databases, covering publications from 2000 to 2025 using boolean operator-based keyword structures: ("osteogenesis imperfecta" OR "brittle bone disease") AND (bisphosphonate OR pamidronate OR zoledronate OR "zoledronic acid" OR alendronate OR risedronate) AND ("drug holiday" OR discontinuation OR cessation OR "off-therapy" OR withdrawal OR "treatment pause").

Article selection is carried out through the stages of identification, filtering based on titles and abstracts using PRISMA flow diagrams, feasibility assessment with full text reading, to the determination of studies that meet the criteria. The inclusion criteria include original research published in English or Indonesian that discusses the effectiveness of drug holidays on long-term therapy in children with OI, while the exclusion criteria include articles without access.

The data extracted included the author's name, year of publication, samples, type of therapy, duration of drug holiday, and outcome (BMD, BTM, and fracture incidence). The free variables in this study were the administration of drug holiday on long-term bisphosphonate therapy, while the bound variables include changes in Bone Mineral Density (BMD), incidence of new fractures or recurrence of fractures, as well as changes in Bone Turnover Markers (BTM). All data were analyzed in narrative synthesis by grouping the results based on study design, key variables, and conclusions related to the effectiveness and safety of temporary cessation of bisphosphonate therapy (drug holiday) in pediatric patients with OI.

3. Results and Discussion

Based on literature search results through the PubMed, Scopus, and Science Direct databases, a total of 423 articles were obtained that were relevant to the search keywords. It consists of 91 articles from Scopus, 27 articles from PubMed, and 305 articles from Science Direct.

Of the total articles obtained, as many as 31 articles were excluded because it was a duplication between databases. Furthermore, the screening process was carried out based on titles and abstracts, and 372 articles were excluded because they did not meet the research variables, did not meet the criteria of inclusion or exclusion, or could not be accessed in full text (full text unavailable). After a feasibility assessment through a full text reading, 9 studies that met the inclusion criteria and were included in the final analysis.

The selection and screening process of the study is shown in the PRISMA flowchart which can be seen in Figure 1.

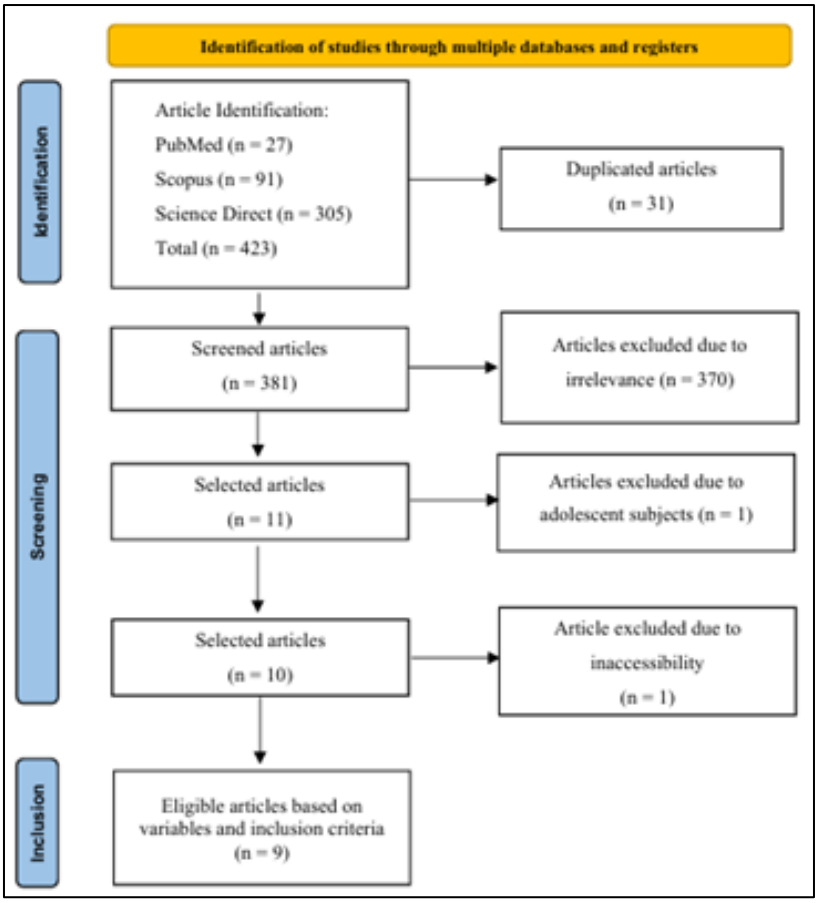

Figure 1 Study selection process

After the article identification and selection process was carried out, ten journals that met the inclusion criteria were then systematically analyzed to assess the effects of discontinuation of bisphosphonate therapy (drug holiday) in children with Osteogenesis Imperfecta (OI).

A summary of the results of each journal review is presented in Table 1, which contains information on study characteristics, research design, number of subjects, duration of drug holiday, as well as key findings related to changes in Bone Mineral Density (BMD), Bone Turnover Marker (BTM), and fracture incidence.

Table 1 Summary of review results

Author (year)	**Title**	**Number of Subjects (child) and types of therapy**	**Conclusion**
Rauch et al. (2007)	Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta	In 23 patients (with an average age of 13.4±4.4 years), the type of therapy received was pamidronate IV	The study found that discontinuing pamidronate for an average of 1.9 years in children with OI led to a significant decline in bone density, particularly in the metaphysis, with marked reductions in BMC, total vBMD, and trabecular vBMD ($p < 0.001$). The decrease in the diaphysis was much smaller (about 0.3 SD; $p < 0.001$). Lumbar spine DXA measurements also showed meaningful reductions: 0.4 SD in BMC ($p = 0.001$), projection area ($p = 0.04$), and aBMD ($p < 0.001$).

Ward et al. (2007)	Can bisphosphonate treatment be stopped in a growing child with skeletal fragility?	1 2-year-old boy, OI type IV, pamidronate	The study concluded that discontinuation of pamidronate in children with OI for ± 24 months led to a very rapid and clinically significant decrease in BMD, demonstrated by a decrease in LS-vBMD from Z-score -1 (after 4.5 years of therapy) to Z-score -3.68 in the 24 months following drug holiday, a value even lower than the pretreatment Z-score (-2.38); a decrease also occurred in RTot-vBMD and RTr-vBMD. During the drug holiday, stress fractures reappeared, including a tibial stress fracture occurring within the first year after stopping treatment.
Bratanic et al. (2015)	CHILDHOOD OSTEOPOROSIS AND PRESENTATION OF TWO CASES WITH OSTEOGENESIS IMPERFECTA TYPE V	2 male child patient type V. Patient 1 was 16 years old at the time of discontinuation of therapy	Patient 1 showed a sustained response after discontinuation of pamidronate therapy, with BMD LS remaining within the normal range for 5 years of discontinuation of therapy.
Rauch et al. (2006)	Pamidronate in Children and Adolescents with Osteogenesis Imperfecta: Effect of Treatment Discontinuation	62 children (OI type I, III, and IV), • Controlled study: 24 patients (12 stop pamidronate, 12 advanced). • Observational study: 38 patients stopped pamidronate	Discontinuation of pamidronate for 2 years in 12 children with OI (control study) led to a decrease in lumbar spine aBMD z-score of 0.4 SD ($p = 0.01$) and a significant increase in bone turnover, indicated by an increase in NTX/Cr ($p = 0.02$) and NTX (% reference) ($p = 0.008$). In the observational cohort, the BMC and projection area increased (both $p < 0.001$) and the aBMD (g/ cm^2) increase slightly ($p = 0.004$), but the z-score decreased significantly ($p = 0.001$). The incidence of fractures was not increased, with fracture rates in control studies not different (13 vs 6; $p = 0.48$) and in observational studies the proportion of fracture patients decreased but was not statistically significant ($p = 0.20$).
Vasanwala RF et al. (2016)	Recurrent Proximal Femur Fractures in a Teenager With Osteogenesis Imperfecta on Continuous Bisphosphonate Therapy: Are We Overtreating?	1 female patient age 13.4 years, OI type IV	After the discontinuation of pamidronate in a girl with type IV OI who had undergone therapy for 7 years, the BMD remained elevated relative to her body size, with the lumbar spine Z-score increasing from -2.7 prior to therapy to -0.6 at the time of discontinuation, and the size-adjusted BMAD Z-score reaching +0.22 earlier during treatment. Following treatment cessation, she sustained two additional non-traumatic proximal femur fractures that fulfilled criteria for atypical femur fractures.
D'Eufemia P et al. (2017)	Serum creatine kinase isoenzymes in children with osteogenesis imperfecta	18 children OI type I (12 advanced therapy, 6 stop nephronate)	D'Eufemia et al. (2017), six OI type 1 children who discontinued neridronate underwent a 2-year drug holiday with the result that BMD remained relatively fluctuating, where the lumbar spine BMD z-score which had previously increased from -2.38 to -0.10 after therapy only decreased slightly to -0.50 at follow-up. CTx bone resorption biomarkers were maintained low and stable throughout

			the observation period (0.87 → 0.75 → 0.89 ng/mL), while CKbb decreased to undetectable, suggesting normalization of osteoclast activity post discontinuation of therapy.
Vuorimies I et al. (2017)	Bisphosphonate Treatment and the Characteristics of Femoral Fractures in Children With Osteogenesis Imperfecta	93 OI type I, III, and IV children with an average age of 7.8 years (1.0 to 18.5 years)	This study showed that bisphosphonates during active therapy and during a drug holiday of ≥1 year did not change the pattern of fracture location or type, shown with statistically meaningless results (P = 0.78 for location and P = 0.35 for fracture type). In contrast, OI type significantly influenced fracture characteristics (P = 0.02), where type III-IV is more likely to experience distal fractures and transverse patterns. In fact, refracture was more prevalent in naïve patients (21%) than those who were on therapy (5%) and those who discontinued therapy (10%).
Robinson ME et al. (2019)	Osteogenesis Imperfecta: Skeletal Outcomes After Bisphosphonate Discontinuation at Final Height	31 OI type I, III-VII patients, with an average age of 16.4 (13.4-20)	This study evaluated 31 OI patients who discontinued bisphosphonate therapy after reaching final height at the age of 13.4-20 years and were followed for 4 years. After discontinuation, the lumbar spine BMD increased by 4% ($p < 0.05$) with the Z-score remaining stable, while the pQCT showed a decrease in trabecular distal radius vBMD (−19%, $p < 0.05$) but an increase in cortical vBMD (+4%, $p < 0.05$). No new vertebral compression fractures were found, and the proportion of patients with long bone fractures decreased significantly from 42% before discontinuation to 16% in the 3rd/4th year ($p < 0.05$).
Zhang et al. (2022)	Skeletal outcomes of patients with osteogenesis imperfecta during drug holiday of bisphosphonates: a real-world study	149 OI type I, III-V patients (127 children, 22 adults), median child age 11.3 years (7.7-15.8)	In 127 children with OI in the study Zhang et al. (2022), which started drug holiday at the median age of 11.3 years after 3.95 years of bisphosphonate therapy. In average 3 years (follow-up 1-7 years) drug holiday BMD LS increased significantly from 0.934 to 0.990 g/cm^2 ($p < 0.001$) in the first year and remained stable for up to 3 years, while Z-score LS did not change significantly. The femoral BMD is relatively stable; although the femoral neck and trochanter Z-scores decreased slightly ($p = 0.03$ and $p = 0.04$), this decrease was not considered clinically meaningful because the changes were so small (about 0.2-0.3 SD). The annual fracture rate decreased significantly from 0.18 to 0.08 fractures/patient/year ($p = 0.01$), and no atypical fractures or ONJ were found. The β-CTX bone turnover marker is mildly increased, but remains within normal limits.

The results of nine studies showed that the temporary cessation of bisphosphonate therapy (drug holiday) in children with Osteogenesis Imperfecta (OI) resulted in a response that varied depending on the age of the child, type of OI, type and duration of therapy, as well as some of the skeletal parameters evaluated.

3.1. Effect of Drug Holiday on Bone Mineral Density (BMD)

Across the nine included studies, the effects of drug holiday on BMD varied substantially depending on OI severity, patient age, and growth phase. Some studies demonstrated clear declines in BMD following treatment discontinuation, particularly among children who remained in rapid growth. Rauch et al. (2006) reported significant reductions in total and trabecular vBMD within 1.9 years of stopping pamidronate (16). While Ward et al. (2007) described a pronounced drop in LS-vBMD—from a Z-score of −1 to −3.68 in a child with OI type IV within 24 months (17). In another study by Rauch et al. (2007), decreases in Z-scores were observed despite increases in absolute aBMD, indicating that skeletal growth exceeded the residual benefits of therapy (18). These findings collectively suggest that children who have uncompleted growth may be vulnerable to losing some of the mineral gains achieved during active therapy once bisphosphonates are withheld (16–18).

In contrast, several studies indicate that BMD can remain stable or even improve after discontinuation, especially among children who have reached final height. Bratanic et al. (2015) reported normal-range BMD up to five years after pamidronate cessation in a patient with OI type V (19). D'Eufemia et al. (2017) found that children with OI type I maintained lumbar spine BMD still fluctuating during a two-year drug holiday (20). Robinson et al. (2019) documented a 4% increase in lumbar spine BMD in patients who had reached final height, and Zhang et al. (2022), the largest study to date, reported significant improvement in lumbar spine BMD during the first year of drug holiday followed by sustained stability for up to three years (11,12). These findings demonstrate that drug holiday can be safely implemented in selected patients particularly who have completed growth though rare complications such as recurrent atypical fractures, as described by Vasanwala et al. (2016), highlight the need for individualized risk assessment (11,12,19–21).

Several factors appear to influence the skeletal response during a bisphosphonate drug holiday in children with OI. One of the most consistent findings is the age at therapy discontinuation, where younger children who remain in an active growth phase demonstrate a more rapid decline in after bisphosphonate discontinuation, because bone turnover increases as the skeleton returns to its untreated physiological state (12,17,18). In contrast, patients who discontinue therapy closer to late puberty when linear growth slows tend to maintain more stable BMD (11). Another contributing factor is the nature of bone formed during the drug holiday, where newly formed bone that has never been exposed to bisphosphonates tends to exhibit lower density, potentially leading to a relative decline in overall BMD (16,18). Overall, drug holidays appear to be safer for children who have reached or are near completion of their growth phase. However, type of OI, according to the available literature has insufficient evidence to establish a clear association with the skeletal response during a drug holiday

3.2. Effect on Drug Holiday on Bone Turnover Markers (BTMs)

Bone Turnover Markers (BTMs), drug holiday affected bone turnover markers differently across studies. Rauch et al. (2006) observed significant elevations in NTX/Cr within two years of stopping therapy, indicating reactivation of osteoclastic activity after prolonged suppression. Such rebound activity may contribute to the declines in BMD reported in this cohorts and need for close monitoring among children with elevated baseline turnover (16).

In contrast, some studies show children consistently maintain low turnover after drug holiday. D'Eufemia et al. (2017) showed that serum CTx levels remained consistently low during a two-year discontinuation period, suggesting sustained residual bisphosphonate effects (20). Similarly, Zhang et al. (2022) reported only a mild rise in β -CTX. Overall, these findings indicate that residual bisphosphonate deposition is sufficient to maintain metabolic stability during drug holiday (11,20).

The variability in BTM findings across the three studies can be explained largely by differences in prior bisphosphonate exposure, age at treatment discontinuation, and methodological variations. Longer treatment duration leads to greater drug accumulation in bone, producing a sustained suppressive effect on bone turnover, as reflected in the stable BTM levels reported by Zhang et al. (2022) (11). In contrast, D'Eufemia et al. (2017) observed notable changes in osteoclast-related markers after treatment cessation, which may be related to the shorter duration of neridronate exposure and the use of different turnover indicators such as CK isoenzymes (20). Rauch et al. (2006) similarly reported only modest fluctuations in NTX and ALP, likely due to heterogeneous treatment duration and baseline turnover among patients (16). Additional variation arises from differences in the specific markers measured and the criteria used to define drug

holiday across studies. Taken together, these factors explain why BTM responses after bisphosphonate discontinuation are inconsistent among published reports (11,16,20).

3.3. Effect on Drug Holiday on Fracture Incidence

Fracture events are the most clinically relevant outcome in Osteogenesis Imperfecta, and the majority of evidence indicates that drug holidays do not increase fracture risk when implemented in appropriate candidates. Several studies consistently demonstrate that discontinuing bisphosphonate therapy does not worsen fracture incidence. Rauch et al. (2006) reported no increase in fractures in either the controlled cohort (13 vs 6, $p = 0.48$) or the observational group ($p = 0.20$) (16). Similarly, Vuorimies et al. (2017) found no significant differences in fracture location or type between children who continued therapy and those on a drug holiday ($P = 0.78$ and $P = 0.35$), emphasizing that OI type rather than bisphosphonate exposure was the principal determinant of fracture characteristics (22). Robinson et al. (2019) further demonstrated a substantial decrease in long-bone fractures following treatment cessation, while Zhang et al. (2022) observed a significant reduction in annual fracture rates from 0.18 to 0.08 fractures per patient per year ($p = 0.01$) (11,12). These findings suggest that the structural improvements achieved during active bisphosphonate therapy are maintained in the short to medium term, and that residual drug effects likely continue even after discontinuation (11,12,16,22).

Despite this overall reassuring pattern, isolated cases highlight potential risks associated with oversuppression of bone remodeling. Vasanwala et al. (2016) described a child with OI type IV who experienced recurrent femoral fractures, including atypical femoral fractures, after long-term pamidronate therapy was discontinued despite persistently high BMD values (21). This case illustrates how prolonged oversuppression may lead to impaired microdamage repair, accumulated structural fatigue, and mechanical fragility when treatment is withdrawn. Such findings underscore the need for individualized assessment before initiating a drug holiday (14,21,23).

4. Conclusion

Drug holidays have the potential to be a safe and effective therapeutic strategy for many children with Osteogenesis Imperfecta (OI), especially in patients with good therapeutic response, adequate BMD improvement, as well as those who have approached or reached the end of growth, but the existing literature provides insufficient data to define a definitive association between OI type and skeletal response during drug holiday periods. Evidence from various studies shows that in this group, bisphosphonate cessation was able to maintain BMD stability and did not increase the incidence of fracture. However, in children with active growth or a history of recurrent fractures, drug holidays may be at risk of causing decreased BMD, increased bone turnover, or the reappearance of fractures. In addition, long-term use of bisphosphonates also has the potential to cause bone remodeling oversuppression which can contribute to atypical fractures. Therefore, the determination of drug holiday should be done based on the specific evaluation of each patient, with close monitoring of BMD, Bone Turnover Markers (BTM), and fracture events to determine the need for retreatment. This approach is expected to provide an optimal balance between therapeutic benefits and potential risks, thereby supporting safer, more targeted, and sustainable management of OI.

Compliance with ethical standards

Acknowledgments

The authors are thankful to the Airlangga University's, Faculty of Medicine for their invaluable assistance in carrying out this study.

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest related to this work.

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