ORIGINAL ARTICLE

Enhancing bone mineral density in osteogenesis imperfecta: The role of zoledronic acid, vitamin D, calcium & phosphate

NISA AFIDATUN HARIROH[1,2], RAYI KURNIA PERWITASARI[1,2], YUNI HISBIYAH[1,2], NUR ROCHMAH[1,2], ROSY SETIAWATI[3], MUHAMMAD FAIZI[1,2]

[1]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [2]Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; [3]Department of Radiology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Background and aim: Osteogenesis imperfecta (OI) is an uncommon genetic condition arising from type I collagen mutations, leading to bone fragility and recurrent fractures. Zoledronic acid is used to improve bone mineral density (BMD). The role of vitamin D, calcium, and phosphate in modulating BMD outcomes remains unclear. This study aimed to assess the effectiveness of zoledronic acid in increasing BMD in children with OI and its association with metabolic factors.

Methods: A retrospective study was conducted on 24 children with OI in East Java. All patients received zoledronic acid (0.05 mg/kg) every 4–6 months for ≥1 year. Clinical data, fracture history, vitamin D, calcium, phosphate, and dual-energy X-ray absorptiometry (DXA) results at baseline and 2 years were analyzed using paired t-test, logistic regression, and correlation tests.

Results: Most subjects were male, diagnosed at 20.0 ± 25.8 months, predominantly OI type III (95.8%). Mean treatment duration was 4.42 ± 2.69 years with a median of eight infusions. Absolute BMD (g/cm²) significantly increased at L1–4 ($p=0.014$), Total Body ($p<0.001$), and TBLH ($p=0.013$), though Z-score changes were not significant. Treatment cycles (OR=1.823; $p=0.022$) and duration (OR=2.572; $p=0.022$) predicted BMD improvement. Vitamin D ($r=0.455$; $p=0.025$) and calcium ($r=0.484$; $p=0.017$) correlated with Z-score BMD TBLH. Vitamin D deficiency was found in 45.8% of patients.

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Correspondence: Nur Rochmah, MD, Pediatrician / Department of Child Health, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Prof. DR. Moestopo street, No.6-8, Airlangga, Kec. Gubeng 60286, Surabaya, Indonesia / E-mail: nur-r@fk.unair.ac.id
ORCID: 0000-0002-9626-9615

Conclusions: Zoledronic acid improves absolute BMD in children with OI, particularly with long-term treatment. Vitamin D status appears to support bone response, highlighting the importance of combined pharmacologic and nutritional management. (www.actabiomedica.it)

Key words: osteogenesis imperfecta, bone mineral density, zoledronic acid, vitamin D, calcium, phosphate

Introduction

Osteogenesis imperfecta (OI) is an uncommon inherited connective tissue disorder distinguished by heightened bone fragility, recurrent fractures, and various skeletal deformities. It is most often attributed to mutations in the COL1A1 and COL1A2 genes, which code for the α1 and α2 chains of type I collagen (1). These genetic alterations disrupt collagen synthesis and extracellular matrix organization, leading to reduced bone strength and increased susceptibility to fractures. The clinical manifestations of OI exhibit considerable variability, spanning from mild forms to severe types that can be fatal in the perinatal period. Worldwide, the estimated incidence ranges from 1 in 10,000 to 25,000 live births, whereas in Indonesia, the reported prevalence is approximately 1 in 20,000 live births (2). In East Java, 37 children with OI have been identified, most with type III disease, which presents early in life with recurrent fractures and severe deformities (2). These findings highlight both the rarity of OI and its substantial clinical burden in pediatric populations. The management of OI necessitates a multidisciplinary approach involving coordinated rehabilitation, orthopedic interventions, and pharmacological treatment. Among available treatments, bisphosphonates remain the standard option. These drugs work by binding to hydroxyapatite in the bone and blocking osteoclast-driven bone breakdown. As a result, they help slow bone turnover and improve bone mineral density (BMD) (3). Among available treatment options, zoledronic acid—a third-generation bisphosphonate—has shown superior potency compared to pamidronate. It promotes an increase in BMD and decreases biochemical markers of bone turnover, as reflected by reduced levels of the N-terminal propeptide of type I procollagen (PINP) (4). These advantages have established zoledronic acid as a preferred agent in pediatric OI management. Despite these benefits, the effect of bisphosphonate therapy on fracture incidence remains controversial. Some studies have reported reductions in fracture frequency after long-term treatment, whereas others found no significant association (5). This inconsistency suggests that additional factors beyond drug therapy may influence fracture risk. Vitamin D, calcium, and phosphate are critical to bone health. Vitamin D facilitates calcium absorption, modulates osteoblast activity, and suppresses parathyroid hormone secretion, while calcium and phosphate form the mineral basis of bone structure and strength (6,7). Deficiencies in these nutrients can further compromise bone integrity and exacerbate fracture risk in OI patients (8). However, few studies have explored the combined impact of zoledronic acid therapy and nutritional status on fracture outcomes, particularly in resource-limited settings such as Indonesia, where deficiencies are more prevalent (9). To bridge this knowledge gap, the present study investigated the relationship between zoledronic acid therapy and improvements in BMD and fracture rates, while also examining the influence of vitamin D, calcium, and phosphate levels in children with OI. By considering both medical treatment and nutritional factors, the study aims to provide a more comprehensive view of fracture risk and guide tailored treatment strategies. Ultimately, the findings are expected to support integrated care approaches that enhance long-term outcomes and quality of life for children with OI in Indonesia.

Patients and methods

Study design and subjects

This retrospective study involved 24 pediatric patients diagnosed with osteogenesis imperfecta (OI) originating from the East Java region. Data were collected during a patient gathering event and supplemented by review of medical records. Inclusion criteria were a confirmed diagnosis of OI based on the Sillence classification and receipt of zoledronic acid therapy for at least one year. Zoledronic acid was administered at 0.05 mg/kg body weight every 4–6 months. Informed consent was obtained from children and their parents/guardians prior to blood sampling. Children with incomplete clinical data or whose parents/guardians declined consent for blood sampling were excluded. This research received ethical clearance from the Health Research Ethics Committee of Faculty of Medicine Universitas Airlangga (Ethic number: 202/EC/KEPK/FKUA/2024). The approval was granted on 10 December 2024 and is valid until 10 December 2025.

Data collection

Clinical and demographic information was gathered through interviews with the patients' parents or legal guardians. Variables recorded included age, sex, OI type, age at diagnosis, gestational age at birth, mode of delivery, fracture history within the previous year, duration and number of zoledronic acid cycles, vitamin D supplementation, and daily sunlight exposure (>1 hour or <1 hour). BMD data, including baseline and follow-up values, were extracted from patient records. BMD was assessed using dual-energy X-ray absorptiometry (DXA; GE Lunar Prodigy) at the lumbar spine (L1–L4), total body, and total body less head (TBLH). Results were expressed in g/cm^2 and Z-scores, with pediatric reference values obtained from the Children's Hospital of Philadelphia calculator. Serum levels of 25-hydroxyvitamin D [25(OH)D], calcium, and phosphate were measured from collected blood samples. Vitamin D levels were measured using chemiluminescent microparticle immunoassay (CMIA; Architect reagents) at Prodia Clinical Laboratory, Surabaya. Vitamin D status was categorized as sufficient (30–100 ng/mL), insufficient (20–29.9 ng/mL), or deficient (<20 ng/mL). Calcium and phosphate were measured using the Siemens Dimension EXL 200 analyzer, and results were interpreted against pediatric reference ranges.

Statistical analysis

Normal distribution was evaluated with the Shapiro-Wilk test. Variables with normal distribution were analyzed using paired t-tests, while those not normally distributed were evaluated with the Wilcoxon signed-rank test. Logistic regression analysis was conducted to explore the association between BMD improvement and either treatment duration or the number of zoledronic acid cycles. The relationships between BMD and serum levels of vitamin D, calcium, and phosphate were examined using Pearson's correlation for normally distributed variables and Spearman's correlation for non-normally distributed variables. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

This study included 24 patients with osteogenesis imperfecta (OI). The majority were male, comprising 14 children (58.3%), while females accounted for 10 children (41.7%). The mean age at the time of study was 8.77 ± 3.81 years, with a mean age at diagnosis of 20.0 ± 25.8 months. According to the Sillence classification, most patients were categorized as type III OI (95.8%), while only one patient (4.2%) was diagnosed with type IV. Regarding perinatal characteristics, the majority of children were born at term (88%), whereas 12% were preterm. In terms of mode of delivery, 15 children (62.5%) were delivered vaginally and 9 children (37.5%) by cesarean section. The baseline characteristics of the participants are summarized in Table 1. A fter assessing data normality, comparisons between baseline and follow-up BMD values were performed using paired t-tests. (Table 2). Bivariate analysis demonstrated significant increases in absolute

Table 1. Baseline characteristics of the study subjects.

Variable (n=24)	Frequency (%)	Mean ± SD	Median (Min–Max)
Duration of Bisphosphonate Therapy (years)		4.42 ± 2.69	
Total Zoledronic Administration (times)			8 (1 – 18)
Fracture Frequency within 1 year (times)			0 (0 – 4)
Bone Mineral Density			
BMD L1-4	12 (50.0)		
Within normal range	12 (50.0)		
Below z-score			
BMD Total Body			
Within normal range	6 (25.0)		
Below z-score	18 (75.0)		
BMD TBLH			
Within normal range	5 (20.8)		
Below z-score	19 (79.2)		
Vitamin D Level (ng/mL) (ng/mL)			21.8 (11.4-113.4)
Sufficiency (30-100 ng/mL)	9 (37.5)		
Insufficiency (20-29 ng/mL)	4 (16.7)		
Deficiency (<20 ng/mL)	11 (45.8)		
Calcium Level (mg/dL):		8.74 ± 0.59	
Normal (8.5-10.5 mg/dL)	20(83.3)		
Decreased	4 (16.7)		
Phosphate Level (mg/dL)		4.35 ± 0.64	
Blood Phosphate Status			
Normal (4.5-5.9 mg/dL)	19 (79.2)		
Decreased	5 (20.8)		
Sunlight Exposure			
More than 1 hour	10 (41.7)		
Less than 1 hour	14 (58.3)		

Abbreviations: BMD: Bone Mineral Density; TBLH: total body less head; SD: standard deviation.

Table 2. Paired t-tested comparing baseline and follow-up Bone Mineral Density

Variable	Mean ± SD Baseline	Mean ± SD Follow-up	Mean ± SD Change from Baseline to Follow-up	*P*-value Bivariate
BMD L1-4				
BMD L1-4 (g/cm^2)	**0.462 ± 0.15**	**0.555 ± 0.22**	**-0.093 ± 0.168**	**0.014***
BMD L1-4 *(Z-score)*	-2.195 ± 2.37	-1.540 ± 3.13	-0.655 ± 2.668	0.251
BMD Total Body				
BMD Total Body (g/cm^2)	**0.567 ± 0.122**	**0.642 ± 0.141**	**-0.074 ± 0.07**	**0.00***
BMD Total Body *(Z-score)*	-3.147 ± 3.214	-2.936 ± 2.945	-0.210 ± 1.42	0.484
BMD TBLH				
BMD TBLH (g/cm^2)	**0.362 ± 0.206**	**0.488 ± 0.142**	**-0.126 ± 0.223**	**0.013***
BMD TBLH *(Z-score)*	-4.548 ± 3.219	-3.669 ± 2.331	-0.879 ± 2.515	0.108

* *p<0.05; Abbreviations:* BMD: Bone Mineral Density; TBLH: total body less head; SD: standard deviation.

Table 3. Multivariate logistic regression analysis of determinants influencing bone mineral density among children with osteogenesis imperfecta.

Independent Variable	B	*P*-value	OR (Exp(B))	95% CI Exp(B)
Total Zoledronic Administration (times)	0.6	**0.022***	**1.823**	1.091 – 3.046
Duration of Bisphosphonate Therapy (years)	0.945	**0.022***	**2.572**	1.151 – 5.743
Vitamin D status	-0.083	0.964	0.920	0.024 – 35.111
Calcium level	0.887	0.593	2.429	0.094 – 63.009
Phosphate level	-0.268	0.914	0.814	0.019 – 34.302
Constant	-5.963	**0.006***	0.003	-

* *p<0.05; Abbreviations:* OR: odds ratio; CI: confidence interval.

Table 4. Correlation analysis in the second (follow-up) measurement demonstrated a significant association between BMD (L1–4, Total Body, and TBLH) and serum levels of vitamin D, calcium, and phosphate.

BMD Variable	Vitamin D level (r.p)[a]	Calcium Level (r.p)[b]	Phosphate Level (r.p)[b]
BMD L1-4 (g/cm^2)	r = -0.254; *p* = 0.232	r = 0.083; *p* = 0.701	r = 0.032; *p* = 0.880
BMD L1-4 (Z-score)	r = -0.050 *p* = 0.816	r = 0.207 *p* = 0.331	r = 0.110 *p* = 0.610
BMD Total Body	r = -0.217; *p* = 0.309	r = 0.317; *p* = 0.131	r = 0.233; *p* = 0.274
BMD Total Body (Z-score)	r = 0.311 *p* = 0.139	**r = 0.407** ***p* = 0.048***	r = 0.350 *p* = 0.093
BMD TBLH	r = -0.161; *p* = 0.451	r = 0.326; *p* = 0.120	r = -0.043; *p* = 0.840
BMD TBLH (Z-score)	**r = 0.455** ***p* = 0.025***	**r = 0.484** ***p* = 0.017***	r = 0.291 *p* = 0.168

* *p<0.05; Abbreviations:* BMD: Bone Mineral Density; TBLH: total body less head.

BMD (g/cm²) at all three measurement sites following zoledronic acid therapy, although changes in Z-scores were not statistically significant.

Multivariate logistic regression analysis was conducted to identify factors associated with bone mineral density among patients with OI (Table 3). The analysis identified several variables that demonstrated a statistically significant association.

The analysis indicated that both the number of zoledronic acid infusions and the overall duration of treatment were important predictors of improved bone mineral density. Children who received therapy for longer periods and more frequent infusions were more likely to achieve bone density levels appropriate for their age. In contrast, biochemical parameters such as vitamin D, calcium, and phosphate concentrations did not demonstrate a significant relationship with bone density outcomes. The correlation analysis revealed that improvements in bone mineral density following zoledronic acid therapy were largely independent of serum vitamin D, calcium, and phosphate levels (Table 4). While most measurements showed no meaningful associations, limited but noteworthy relationships were observed between bone density scores and both calcium and vitamin D at specific skeletal sites. Overall, these results suggest that zoledronic acid plays a central role in enhancing bone density in children with osteogenesis imperfecta, whereas the

contribution of biochemical markers appears modest and site-specific.

Discussion

This study demonstrates that zoledronic acid therapy significantly increases absolute bone mineral density (BMD) at multiple skeletal sites, including the lumbar spine (L1–4), total body, and total body less head (TBLH), in children with osteogenesis imperfecta (OI). These findings are consistent with previous research confirming the efficacy of bisphosphonates in pediatric OI. Early studies by Glorieux (10) and Rauch and Glorieux (11) provided the foundation for bisphosphonate use in this population, while more recent work by Martanto et al. (12) similarly demonstrated significant improvements in lumbar and total body BMD following two years of zoledronic acid therapy. The current results further reinforce the role of zoledronic acid as an effective treatment modality for improving bone mass in children with OI. An important finding of this study is that although absolute BMD increased significantly, improvements in Z-scores were less pronounced. This discrepancy likely reflects the extremely low baseline BMD values in this cohort as well as heterogeneity in patient age. Because Z-scores are normalized to age- and sex-specific reference standards, patients starting with severely depressed BMD values may show marked absolute improvements without achieving normalization. This phenomenon has been described previously and is consistent with findings reported by Coccia et al. (13), who noted that relative gains in BMD may underestimate treatment benefits in populations with heterogeneous baselines. Thus, the results suggest that zoledronic acid improves bone mineralization substantially, but many children remain below expected reference standards, underscoring the need for prolonged therapy and adjunctive interventions.

Treatment duration and cumulative effect

Multivariate logistic regression confirmed that both the number of zoledronic acid infusions and longer treatment duration independently predicted improved BMD outcomes. These findings support the concept of a cumulative effect, whereby repeated exposure to zoledronic acid progressively enhances skeletal outcomes. Comparable results have been documented in several international studies. For instance, Vuorimies et al. (14) reported sustained increases in lumbar BMD with successive intravenous infusions, while Riaz et al. (15) demonstrated significant improvements in bone density with prolonged bisphosphonate therapy in pediatric OI cohorts. The present findings therefore highlight that both adequate treatment duration and adherence to infusion schedules are crucial for maximizing therapeutic benefits. Although fracture incidence was not analyzed statistically, a downward trend in new fracture frequency was observed, aligning with the work of Pulungan et al (5) in Indonesian children with OI. This trend, though preliminary, suggests that structural improvements in bone mass may translate into clinically meaningful reductions in fracture risk. Future prospective studies with fracture incidence as a primary endpoint are warranted to clarify this relationship.

Role of vitamin D and mineral homeostasis

Aside from pharmaceutical treatments, the study also examined how vitamin D, calcium, and phosphate levels influence bone health. Vitamin D plays a crucial role in maintaining skeletal function through several mechanisms. It enhances calcium absorption in the intestines, regulates the development of osteoblasts (the cells responsible for building bone), and suppresses parathyroid hormone release. In addition, vitamin D directly affects gene activity by binding to the vitamin D receptor (VDR). Genes such as *ALPL* and *BGLAP*, which are involved in osteoblast maturation and matrix mineralization, are modulated by vitamin D signaling (16). Active $1,25(OH)_2D$ further influences bone remodeling via modulation of the RANKL–OPG system and the Wnt/β-catenin pathway (17). Experimental data reinforce these pathways, demonstrating that vitamin D supplementation enhances the OPG/RANKL ratio, reduces bone resorption, and improves trabecular architecture (18). Clinically, the present study found limited but notable associations between vitamin D and calcium with BMD Z-scores,

particularly at the TBLH site. This suggests that while zoledronic acid exerts a strong independent effect on bone mass, adequate nutritional status may enhance treatment responses at specific skeletal regions. These findings are consistent with (19), who also reported that vitamin D status modulates BMD outcomes in children with OI. However, other investigations, such as those by Plante et al. (20) and Valeeva et al. (21), have reported inconsistent associations, likely reflecting differences in study populations, vitamin D thresholds, assay methodologies, and treatment protocols. Importantly, nearly half of the participants in this study were vitamin D deficient, underscoring the clinical relevance of optimizing vitamin D status in OI management. Given Indonesia's tropical climate, such deficiencies may seem counterintuitive but are well documented in pediatric populations due to limited sunlight exposure, darker skin pigmentation, and dietary insufficiency. The present findings suggest that ensuring adequate vitamin D and calcium may enhance skeletal responses to zoledronic acid, supporting an integrated approach that combines pharmacological and nutritional interventions.

Clinical and public health implications

The debate regarding optimal thresholds for vitamin D sufficiency remains ongoing. The Institute of Medicine (7) defines deficiency as serum concentrations below 20 ng/mL and adequacy as levels above 50 nmol/L, whereas the Endocrine Society advocates for individualized targets based on risk profiles rather than universal cutoffs. Pediatric guidelines, such as those issued by the Royal Children's Hospital, recommend maintaining serum vitamin D above 50 nmol/L while monitoring calcium, phosphate, and parathyroid hormone to ensure balanced mineral metabolism (22). The present findings further support these pediatric-focused recommendations, as higher vitamin D status was associated with better BMD responses. For clinicians, these results highlight the need to view bisphosphonate therapy not as a stand-alone intervention but as part of a broader management strategy. Routine assessment and correction of vitamin D and calcium status should be incorporated into OI care, particularly in low- and middle-income countries where nutritional deficiencies are common. Integration of nutritional optimization with pharmacological treatment could improve bone outcomes and reduce the long-term burden of fractures and disability in this vulnerable population. This study contributes valuable evidence from an underrepresented population, as most research on bisphosphonate therapy in OI originates from Western settings. By examining the interaction between zoledronic acid therapy and nutritional status, the study provides insights relevant to clinical practice in Indonesia and similar contexts. Nevertheless, several limitations must be acknowledged. The retrospective design limits causal inference, and the relatively small sample size may reduce statistical power. Fracture incidence, although recorded, was not analyzed as a primary outcome, precluding firm conclusions about clinical fracture risk reduction. Additionally, potential confounders such as physical activity, dietary intake, and adherence to supplementation were not systematically controlled. Despite these limitations, the findings underscore the importance of integrating pharmacological and nutritional strategies in OI management.

Conclusions

In summary, zoledronic acid therapy significantly improves absolute BMD in children with OI, with treatment duration and cumulative number of infusions emerging as independent predictors of skeletal response. While gains in absolute BMD are robust, normalization of Z-scores remains limited, reflecting severe baseline deficits and heterogeneity across patients. Vitamin D and calcium status show site-specific associations with bone outcomes, suggesting that nutritional sufficiency enhances therapeutic efficacy. Together, these findings highlight the need for comprehensive management strategies that integrate long-term bisphosphonate therapy with nutritional optimization. Such an approach holds promise for improving skeletal health and quality of life in children living with OI, particularly in resource-limited settings such as Indonesia.

Ethic Approval: This study received approval from the Health Research Ethics Committee of Faculty of Medicine Universitas Airlangga (Approval No. 202/EC/KEPK/FKUA/2024) and was

conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained for every participant from a parent or legal guardian. The ethical approval was granted on December 10, 2024, and is valid until December 10, 2025.

Conflict of Interest: All authors affirm that they hold no financial or commercial ties that could be considered to influence or create conflict of interest regarding the content of this submitted manuscript.

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