

Effects of Long-Term Pamidronate Treatment on Bone Density and Fracture Rate in 65 Osteogenesis Imperfecta Patients

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What is already known on this topic?

- Osteogenesis imperfecta (OI) is a heterogeneous disease characterized by recurrent fractures. Pamidronate is known to have beneficial effect in patients with OI.

What this study adds on this topic?

- We presented long-term followup findings in a large cohort of patients with OI and showed that cyclic pamidronate treatment decreased the number of fractures and increased bone mineral density (BMD) in patients with OI type 1, 3, and 4.
- We also demonstrated that pamidronate treatment improved platyspondyly, and protected from deformities in all patients with OI.

ABSTRACT

Objective: Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous disease characterized by recurrent fractures, blue sclera, and hearing loss. Bisphosphonate treatment has been reported to decrease the annual number of fractures and improve the quality of life in patients with OI. The aim of this study is to evaluate the effect of bisphosphonate treatment in the Turkish OI cohort.

Methods: Sixty-five patients with OI, who were treated with pamidronate, were included in this study. The mean treatment duration was 47.1 ± 40 months (range:12-168 months). Bone mineral densitometry (BMD) and the mean number of annual fractures were compared before and after the treatment within groups, and the difference after treatment compared between the OI types.

Results: After pamidronate treatment, a significant decrease in the mean annual fracture, along with an increase in BMD Z-score was detected in all patients. Treatment duration did not affect BMD Z-score. However, there was a significant decrease in the mean annual number of fractures after 5 years of treatment ($P = .048$). After treatment, the decrease in the number of fractures was significant in OI type 3, and the increase in BMD Z-score was significant in OI type 4 when compared with OI type 1. Besides, pamidronate treatment relieved pain, and also corrected the platyspondyly radiologically in all OI groups.

Conclusion: We demonstrated that pamidronate treatment improves the quality of life by reducing the number of fractures, relieving pain, and also protecting from deformities in all patients with OI.

Keywords: Bone density, Osteogenesis imperfecta, pamidronate

INTRODUCTION

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a hereditary disease characterized by recurrent bone fractures, blue sclera, hearing loss, short stature, and bone deformities.¹ OI is caused by the defects in the synthesis or processing of type 1 collagen, which is the main structural protein of bones, tendons, sclera, and teeth. OI is a clinically heterogeneous disease; besides the perinatal lethal types, there are also milder phenotypes characterized by osteopenia.² The prevalence of the disease is between 1/15 000 and 1/20 000. The actual prevalence may be higher, as some mild types may not have been diagnosed.³

Sillence et al.⁴ classified OI into 4 groups in 1979. According to this classification, type 1 is a mild form with the blue sclera, type 2 is a perinatal lethal form, type 3 is a severe and progressively deforming form, and type 4 is a moderate form with normal sclera. In

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90% of patients, heterozygous mutations in genes encoding α -1 and α -2 chains of type-1 collagen (*COL1A1* and *COL1A2*) are detected. The severity of the disease is associated with the location and also the type of the mutation.⁵ In recent years, several OI genes have been discovered which are involved in collagen metabolism, bone mineralization, and differentiation. To date, 21 phenotypes and a total of 19 genes including *COL1A1* and *COL1A2* are described in the Online Mendelian Inheritance in Man database.⁶

The decrease in the number of fractures, relief of pain, and prevention of bone deformities are the major goals of treatment in OI. Cyclic bisphosphonate treatment decreases bone resorption by inhibiting osteoclast activity with the effect of the pyrophosphate analog.⁷ Between 1992 and 1997, Glorieux et al.⁸ treated 30 children with cyclic pamidronate therapy. They showed a significant increase in bone mineral density (BMD), radiological improvement, decreased number of fractures, and a slight increase in growth after pamidronate treatment. Bisphosphonates were also found to have an effect on bone histology; increase in bone cortex, trabecular bone tissue, and calcified cartilage tissue were detected after treatment.⁹

The aim of this study to describe the clinical and radiological characteristics of patients with OI type 1, type 3, or type 4 phenotypes, to compare the mean annual number of fractures and BMD within and between groups, to evaluate the pain and skeletal deformities, and to show the effect of bisphosphonate treatment in the Turkish OI cohort.

METHODS

Patients

Sixty-five patients with OI who were followed up in the Istanbul University-Cerrahpasa Pediatric Genetic Department between 1999 and 2016 were enrolled in this study. The diagnosis of OI was based on the clinical (recurrent fractures, blue sclera, dentinogenesis imperfecta), and radiological findings. The male : female ratio was 1 : 1. The median age of onset of symptoms was 7.5 months (range: 1-324 months) and the median age of admission was 41 months (range: 1-480 months). Patients were classified according to Silience et al.⁴ Patients with 1 or less fractures per year were grouped as OI type 1, with 1-3 fractures were grouped as OI type 4, and those with more than 3 fractures or with severe bone deformities were grouped as OI type 3.

We did not have any type 2 patients who received treatment. Thirty-seven patients were classified with type 1 (%57), 15 with type 3 (23%), and 13 with type 4 (20%) (Table 1).

The mean follow-up duration was 87.2 ± 49.3 months (range:18-192 months).

Physical examination included growth parameters, joint range of motion, ophthalmologic, auditory, and dental examinations. Skeletal radiographs, BMD, and biochemical parameters were assessed at diagnosis and in the follow-up. The data on number of fractures, BMD Z-score, and the presence of pain were retrieved from medical records. The bowing of the extremities, presence of wormian bones, platyspondyly, costa deformities, metaphyseal widening, and osteopenia were investigated from the radiographs. The number and the location of fractures, BMD Z-score, and the presence of pain were compared within and between groups.

TREATMENT PROTOCOL

BMD at L1-L4 lumbar vertebrae were assessed by dual-energy X-ray absorptiometry (DXA, QDR 4500W; Hologic Inc., Bedford, Mass., USA); the results were presented in Z scores, as standard deviation units relative to the mean values for equipment-specific age- and sex-matched reference population. The patients who had BMD Z-score at L1-L4 vertebrae lower than -2.5 received pamidronate treatment. The mean treatment duration was 47.1 ± 40 months (range 12-168 months). Thirty-two patients (49.3%) received treatment between 1 and 2 years, 20 patients (30.7%) between 3 and 5 years, and 13 patients (20%) for more than 5 years (Table 1). Cyclic pamidronate was administered at a dose of 1.5 mg/kg every 3 months, intravenously. Pamidronate doses were prepared within 100 ml of normal saline solutions and infused for 3-hour periods. The patients were also given daily doses of 1000 mg calcium carbonate and 400 IU vitamin D replacements.

Statistical Analysis

The statistical analyses were performed by Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). The percentages, standard deviation score, mean, and median values were calculated. The Wilcoxon signed-ranked test was used for intragroup comparison of outcomes before and after the treatment, and the Kruskal-Wallis test was used in the comparisons of the 3 OI groups. Dunn's post hoc test was performed in the pairwise comparisons of significant results. A value of $P < .05$ was considered statistically significant.

Ethics Committee approval was received from the ethics committee of Istanbul University-Cerrahpasa (Date: July 9, 2015, Number:218800). All study procedures were performed following the Declaration of Helsinki.

RESULTS

Comparison of Clinical Findings Before and After Treatment

The mean number of annual fractures and the BMD Z-scores were compared before and after treatment within groups (Table 2). The mean number of fractures was 1.53 before treatment while it was 0.57 ($P < .05$) after treatment in all groups. According to Silience groups, the mean annual fracture rate decreased significantly from 1.04 to 0.33 ($P = .0001$) in type 1; from 2.39 to 0.69 ($P = .013$) in type 3, and from 2.21 to 0.83 ($P = .015$) in type 4 patients after treatment (Table 2). The decrease

Table 1. Distribution of the Duration of Treatment by Clinical Types of Patients

Clinical Type	Treatment Duration			Total, n (%)
	1-2 years	3-5 years	More than 5 years	
Type 1	23	9	5	37 (57 %)
Type 3	4	7	4	15 (23 %)
Type 4	5	4	4	13 (20 %)
Total	32	20	13	65 (100 %)

Table 2. Comparison of the Number of Bone Fractures, BMD Values, and Z-Scores Before and After Treatment in all Patients and within OI Groups

Annual Mean Fracture	All Patients	Type 1	Type 3	Type 4
Before Treatment	1.53 ± 1.3	1.04 ± 1.26	2.39 ± 1.13	2.21 ± 1.35
After Treatment	0.57 ± 0.61	0.33 ± 0.58	0.69 ± 0.61	0.83 ± 0.54
<i>P</i> *	.0001	.0001	.0013	.015
BMD value (gr/cm ²)				
Before Treatment	0.396 ± 0.21	0.468 ± 0.22	0.276 ± 0.14	0.298 ± 0.15
After Treatment	0.572 ± 0.20	0.631 ± 0.22	0.45 ± 0.17	0.558 ± 0.15
<i>P</i> *	.0001	.0001	.04	.002
BMD Z-score				
Before Treatment	-4.07 ± 1.6	-3.66 ± 1.29	-4.96 ± 1.80	-4.34 ± 2.01
After Treatment	-1.66 ± 1.4	-1.63 ± 0.83	-2.47 ± 2.07	-0.68 ± 1.60
<i>P</i> *	.0001	.0001	.006	.002

*The annual mean fracture and BMD values were compared within groups before and after treatment, using the Wilcoxon signed-ranked test.

in the mean fracture number was significantly higher in OI type 3 when compared with type 1 ($P = .007$) (Table 3)

The mean BMD values increased from 0.396 gr/cm² to 0.572 gr/cm² after treatment. BMD values increased from 0.468 gr/cm² to 0.631 gr/cm² ($P = .0001$) in type 1, from 0.276 gr/cm² to 0.45 gr/cm² ($P = .04$) in type 3, and from 0.298 gr/cm² to 0.558 gr/cm² in type 4 patients ($P = .002$) (Table 2). Similarly, the mean BMD Z-scores increased from -4.07 to -1.61 after treatment ($P = .0001$). The mean BMD Z-scores increased from -3.66 to -1.63 ($P = .0001$) in type 1, from -4.96 to -2.47 ($P = .006$) in type 3, and from -4.34 to -0.68 ($P = .002$) in type 4 patients (Table 2). The increase in the BMD Z-score after treatment was significantly higher in OI type 4 than type 1 ($P = .030$) (Table 3)

The mean annual number of fractures and BMD were evaluated according to the duration of treatment. Treatment duration did not affect BMD Z-score; however, there was a significant decrease in the mean annual number of fractures after 5 years of treatment ($P = .048$) (Table 4, Figure 1).

Patients were also evaluated for pain status. Pain relief was determined in 50 patients (76.9%). All patients with type 4, 27 patients with type 1, and 10 patients with type 3 OI had pain relief (Table 5).

Table 3. Comparison of the Difference in the Mean Number of Fractures Annually, BMD Values, and Z-Scores After Pamidronate Treatment, Between OI Groups

	Type 1	Type 3	Type 4	<i>P</i>	Post hoc <i>P</i> ^a
Decrease in the Mean Annual Fracture	0.70 ± 1.32	1.70 ± 1.3	1.38 ± 1.57	.005	$P^{1,3} = .007$; $P^{1,4} = .168$; $P^{3,4} = 1.0$
Increase in the BMD Value (gr/cm ²)	0.18 ± 0.14	0.20 ± 0.13	0.25 ± 0.14	.338	
Increase in the BMD Z-Score	2.03 ± 1.29	2.49 ± 1.85	3.65 ± 1.71	.033	$P^{1,3} = 1.0$; $P^{1,4} = .030$; $P^{3,4} = .18$

^aThe annual mean fracture and BMD values were compared between groups by the Kruskal-Wallis test.
^bDunn's post hoc test was performed in the pairwise comparisons. 1: OI type 1, 3: OI type 3, 4: OI type 4.

Comparisons of Radiological Findings Before and After Treatment

Twenty-two patients had platyspondyly, classified as mild, moderate, or severe. There was severe platyspondyly in 50%, moderate platyspondyly in 45.4%, and mild platyspondyly in 4.6% of these patients before treatment. After treatment, 60% of patients with severe platyspondyly improved to the moderate, and 30% improved to the mild group (Figure 2). In one case, there was no change in platyspondyly. All patients who had moderate platyspondyly improved to the mild group.

DISCUSSION

The response to treatment according to BMD Z-score, the annual number of fractures, OI types, and treatment duration were evaluated in 65 patients with OI. Patients were treated with pamidronate, with a mean treatment duration of 47.1 ± 40 months. In all groups, there was a significant increase in BMD Z-scores after treatment. Moreover, the mean number of fractures annually was decreased from 1.53 ± 1.38 before treatment to 0.57 ± 0.77 after treatment. It is known that bisphosphonate therapy reduces the annual fracture rate in patients with OI, prevents bone deformities, and prevents orthopedic problems.^{10,11,12,13,14} Pamidronate was also reported to be effective in patients younger than 3 years of age. Administration of cyclic pamidronate treatment to this age group resulted in a significant increase in BMD and a decrease in the number of fractures.^{15,16} In addition to the lower fracture rate and higher BMD Z-scores, surgical interventions were also reduced after pamidronate treatment.¹⁷ Unlike these studies, fracture rate remained similar before and after treatment in a study which was attributed to the increased activity of patients.¹⁸

In our study, the effect of the treatment duration on the mean annual number of fractures and BMD Z-scores was evaluated.

Table 4. Number of Bone Fractures, BMD Values, and Z-Scores According to Treatment Duration

Treatment Duration	Mean Annual Fracture			BMD gr/cm ²			BMD Z-Score		
	Before	After	<i>P</i>	Before	After	<i>P</i>	Before	After	<i>P</i>
1–2 years	1.15 ± 1.04	0.46 ± 0.65	>.05	0.443 ± 0.22	0.587 ± 0.22	>.05	-3.69 ± 1.59	-1.23 ± 1.30	>.05
3–5 years	1.76 ± 1.63	0.91 ± 1.04	>.05	0.332 ± 0.19	0.510 ± 0.19	>.05	-4.68 ± 1.63	-2.13 ± 1.85	>.05
5 years and more	2.12 ± 1.51	0.34 ± 0.32	.048	0.387 ± 0.21	0.632 ± 0.17	>.05	-3.97 ± 1.45	-1.68 ± 0.93	>.05

*The annual mean fracture and BMD values were compared within groups before and after treatment, with the Wilcoxon signed-ranked test.

Table 5. Evaluation of Pain Status After Treatment According to the Patients' Clinical Types

Clinical Type	Relief, n (%)	No relief, n (%)	Total, n
Type 1	27 (72.9 %)	10 (28.1 %)	37
Type 3	10 (66.6 %)	5 (33.3 %)	15
Type 4	13 (100 %)	0	13
Total	50 (76.9 %)	15 (23.1 %)	65

The mean annual number of fractures decreased significantly after a 5-year treatment duration ($P = .048$). Similarly, the fracture rate was reduced after the 4-year treatment period but BMD Z-scores were not correlated with the duration of treatment.¹⁹ Interestingly, it is also reported that the fracture rate was significantly increased in patients who received pamidronate for longer than 3 years than the patients who received it for less than 3 years.²⁰

It has been reported that pamidronate treatment was related to improved vertebral height.²¹ Platyspondyly was improved in all patients except 1 in our study. In a study of 37 OI patients, a significant increase in BMD Z-scores, as well as a decrease in vertebral fracture rate were identified after treatment.²²

The decrease in the number of fractures and improvement in BMD Z-scores were significant in types 1, 3, and 4 in the current study. After treatment, OI type 3 patients had a significant decrease in the mean number of annual fractures and OI type 4 patients had a significant increase in the BMD Z-scores when compared with OI type 1.

In one study,¹⁴ the mean number of fractures after a 1-year treatment period was evaluated according to OI types 1, 3, and 4, and the treatment was found to be less effective than in our study. A recent study that evaluated pain scores before and after treatment found that pamidronate treatment significantly reduced the pain scores in children with OI.²³

Our study also showed that pamidronate treatment mainly reduced the complaints of pain in patients.

In recent years, new medical treatment modalities have been found to benefit OI. The effects of treatment with other forms of bisphosphonate were compared, by administering oral alendronate and cyclic pamidronate. In both groups, after 12-18 months of the treatment period, BMD Z-scores were increased and bone turnover markers were decreased. However, there was no significant decrease in the number of fractures in both groups.²⁴ Oral risedronate treatment in patients with OI was compared with the placebo group, and results showed a significant increase in the BMD Z-scores and a decrease in the annual fracture rate. A recent prospective study also showed that monthly IV alendronate was as effective as cyclic pamidronate without any side effects.²⁵ Denosumab, the nuclear kappa receptor activator, was shown to increase the BMD Z-scores and decrease the number of fractures in postmenopausal women. In the studies conducted in small OI patient groups, denosumab was shown to increase BMD Z-scores, increase mobility, and vertebral height.²⁶ Although many drugs have been tried in OI treatment in recent years, pamidronate is still one of the most important drugs.

CONCLUSION

In conclusion, pamidronate treatment is effective in increasing bone density and decreasing the number of fractures in OI patients. In this study, the effect of pamidronate treatment was demonstrated in all OI groups in a large cohort of patients from a single center.

Our study had a few limitations. Patients' life quality was not evaluated; we did not use a scala or scoring system to assess patients' pain. However, the strength of this study is the long follow-up period in a large patient population.

Ethical Committee Approval: Ethics Committee approval was received for this study from the ethics committee of Istanbul University- Cerrah-pasa (Date: July 9, 2015, Number:218800).

Informed Consent: Informed consent was not obtained due to the retrospective design of this study.

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REFERENCES

- Forlino A, Marini JC. Osteogenesis imperfecta. *Lancet*. 2016;387(10028):1657-1671. [CrossRef]
- Sillence DO, Lamande SR. Evaluation of the present understanding of the clinical and genetic heterogeneity and molecular and biochemical basis of osteogenesis imperfecta. In: Saphiro J. R., Byers P. H., Francis H, eds. *Osteogenesis Imperfecta, A Translation Approach to Brittle Bone Disease*. Baltimore: Elsevier; 2014:6-7.
- Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. *Eur J Endocrinol*. 2020;183(4):R95-R106. [CrossRef]
- Sillence DO, Rimoin DL, Danks DM. Clinical variability in osteogenesis imperfecta-variable expressivity or genetic heterogeneity. *Birth Defects Orig Artic Ser*. 1979;15(5B):113-129.
- Gautieri A, Vesentini S, Redaelli A, Buehler MJ. Single molecule effects of osteogenesis imperfecta mutations in tropocollagen protein domains. *Protein Sci*. 2009;18(1):161-168. [CrossRef]
- Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine. *World Wide Web*. <https://omim.org/>. Johns Hopkins University (Baltimore, MD). 2021.
- El-Gazzar A, Högl W. Mechanism of bone fragility: from osteogenesis imperfecta to secondary osteoporosis. *Int J Mol Sci*. 2021;22(2):625. [CrossRef]
- Glorieux FH, Bishop NJ, Plotkin H, et al. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med*. 1998;339(14):947-952. [CrossRef]
- Misof BM, Roschger P, Baldini T, et al. Differential effects of alendronate treatment on bone from growing osteogenesis imperfecta and wild-type mouse. *Bone*. 2005;36(1):150-158. [CrossRef]

10. Philippi CA, Remington T, Steiner RD. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2008;4(4):CD005088.
11. Ying ZM, Hu B, Yan SG. Oral bisphosphonate therapy for osteogenesis imperfecta: a systematic review and meta-analysis of six randomized placebo-controlled trials. *Orthop Surg*. 2020;12(4):1293–1303. [\[CrossRef\]](#)
12. Bembi B, Parma A, Bottega M, et al. Intravenous pamidronate treatment in osteogenesis imperfecta. *J Pediatr*. 1997;131(4):622–625. [\[CrossRef\]](#)
13. Aström E, Söderhäll S. Beneficial effect of bisphosphonate during five years of treatment of severe osteogenesis imperfecta. *Acta Paediatr*. 1998;87(1):64–68. [\[CrossRef\]](#)
14. Lindahl K, Kindmark A, Rubin CJ, et al. Decreased fracture rate, pharmacogenetics and BMD response in 79 Swedish children with osteogenesis imperfecta types I, III and IV treated with pamidronate. 2016;87:11–18.
15. Plotkin H, Rauch F, Bishop NJ, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab*. 2000;85(5):1846–1850. [\[CrossRef\]](#)
16. DiMeglio LA, Ford L, McClintock C, Peacock M. Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. *Bone*. 2004;35(5):1038–1045. [\[CrossRef\]](#)
17. Zacharin M, Kanumakala S. Pamidronate treatment of less severe forms of osteogenesis imperfecta in children. *J Pediatr Endocrinol Metab*. 2004;17(11):1511–1517. [\[CrossRef\]](#)
18. Falk MJ, Heeger S, Lynch KA, et al. Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics*. 2003;111(3):573–578. [\[CrossRef\]](#)
19. Aström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child*. 2002;86(5):356–364. [\[CrossRef\]](#)
20. Mohsenzade P, Amirhakimi A, Honar N, et al. Bone density, fractures and associated factors in Iranian children and adolescents with osteogenesis imperfecta. *BMC Pediatr*. 2021;21(1):37. [\[CrossRef\]](#)
21. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH. Vertebral morphometry in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate treatment. *Bone*. 2006;39(4):901–906. [\[CrossRef\]](#)
22. Palomo T, Fassier F, Ouellet J, et al. Intravenous bisphosphonate therapy of young children with osteogenesis imperfecta: skeletal findings during follow up throughout the growing years J Bone miner. *Resources*. 2015;30:2150–2157.
23. Garganta MD, Jaser SS, Lazow MA, et al. Cyclic bisphosphonate therapy reduces pain and improves physical functioning in children with osteogenesis imperfecta. *BMC Musculoskelet Disord*. 2018;19(1):344. [\[CrossRef\]](#)
24. DiMeglio LA, Peacock M. Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. *J Bone Miner Res*. 2006;21(1):132–140. [\[CrossRef\]](#)
25. Harada D, Kashiwagi H, Ueyama K, et al. Monthly intravenous alendronate treatment can maintain bone strength in osteogenesis imperfecta patients following cyclical pamidronate treatment. *J Pediatr Endocrinol Metab*. 2020;33(11):1391–1397. [\[CrossRef\]](#)
26. Shaker JL, Albert C, Fritz J, Harris G. Recent developments in osteogenesis imperfecta. *F1000Research*. 2015;4(F1000 Faculty Rev):681. [\[CrossRef\]](#)