

## EFFECT OF TREATMENT WITH BISPHOSPHONATES ON CARDIOPULMONARY DYSFUNCTION IN OSTEOGENESIS IMPERFECTA

By

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### ABSTRACT

**Background:** *Osteogenesis Imperfecta (OI) refers to a phenotypically and genetically heterogeneous group of Mendelian disorders that typically manifest with increased bone fragility, recurrent fractures, bone deformities, short stature, hearing loss, and joint laxity.*

**Objective:** *To assess the effect of treatment with bisphosphonates on cardiac and pulmonary functions in patients with Osteogenesis Imperfecta.*

**Patients and Methods:** *This is a cross-sectional study was conducted on 28 OI patients; echocardiography and pulmonary function tests of these patients were studied at the time of recruitment. Sixteen of the studied subjects had baseline echocardiography conducted before starting bisphosphonate therapy. The effect of bisphosphonate therapy on cardiac anatomy and functions was studied by comparing different echocardiographic parameters before and after bisphosphonate therapy in the studied subjects.*

**Results:** *Pulmonary function test results showed that ten patients (38.5%) had restrictive lung disease, two patients (7.7%) had mixed obstructive and restrictive lung patterns, and 14 patients (53.8%) had normal pulmonary function tests. Echocardiography of the studied subjects showed that two patients (7.1%) had increased AO/LA ratio, one patient (3.6%) had hypertrophied IVSd, three patients (10.7%) had hypertrophied IVSs, seven patients (25%) had dilated LVEDD, and four patients (14.3%) had dilated LVESD. All patients had normal systolic function. Five patients (17.9%) had mild mitral, tricuspid and aortic valves regurge. A significant decrease in the median aortic z-score and a significant increase in the median z-scores of IVSd, IVSs, LVEDD, LVESD, LVPW<sub>s</sub> and LVPW<sub>d</sub> were observed after 12 months of bisphosphonate therapy. Meanwhile, there was no significant difference of mean EF, FS & AO/LA ratio before and after treatment. Two cases had impaired EF at baseline and after treatment EF became normal.*

**Conclusion:** *OI had variable pathologic cardiac effects as aortic root enlargement, left atrial enlargement and two cases of impaired left ventricular ejection fraction at baseline that became normal after treatment. Otherwise, OI was not reported to have a significant effect apparently on intraventricular septum and left ventricular volumetric parameters in systole or diastole. Bisphosphonate therapy had a significant effect on the score of aortic root and ejection fraction (which improved significantly). However, treatment with bisphosphonates could not protect against the progressive effects of OI on cardiac muscle with time as the percentage of patients with impaired left ventricular volumetric parameters in systole or diastole increased significantly during follow-up. The most common pulmonary disease in OI children was the restrictive pattern and it was explained by the skeletal deformities of the chest wall and spine.*

**Keywords:** *Bisphosphonates therapy, Osteogenesis Imperfecta, Echocardiography, pulmonary function test.*

## INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder of connective tissues caused by an abnormality in the synthesis or processing of type I collagen (Uttarilli et al., 2019). The primary defect in OI lies in the disturbance of the production and/or subsequent assembly of collagen type I by osteoblasts. Collagen type I is present in many tissues. As a consequence, mutations in the COL1A1 or COL1A2 genes do not only affect bone but other tissues containing collagen type I as well (Nijhuis et al., 2019).

OI is a heterogenous disorder with significant variation in clinical features and severity. Type I OI is characterized by non-deforming fractures, which result from minor trauma and primarily occur in childhood and adolescence.

OI affects mainly left sided cardiac structures with the most commonly reported cardiovascular abnormality is aortic root dilation followed by aortic regurgitation, mitral regurgitation and mitral valve prolapse (Khashu et al., 2006).

Pulmonary complications range from pulmonary hypoplasia causing neonatal death to restrictive lung disease to pulmonary hypertension. Pulmonary impairment, commonly caused by restrictive lung physiology in patients with OI, may cause shortness of breath and lower-respiratory infections (Turkalj et al., 2017).

Bisphosphonates (BPs), synthetic analogues of inorganic pyrophosphate, have been widely used to treat OI. They increase bone mineral density (BMD) and decrease bone turnover biomarkers (Xu et al., 2016).

The effect of (BPs) treatment on cardiac and pulmonary manifestations of patients with OI needs further studying.

### **AIM OF THE STUDY**

The aim of the study is to describe the cardiopulmonary characteristics of OI patients and to assess the effect of treatment with bisphosphonates on cardiac functions in patients with OI.

### **PATIENTS AND METHODS**

#### **Ethical Considerations:**

1. A written informed consent was obtained from patients or their legal guardians.
2. An approval by the local ethical committee was obtained before the study. Approval number 67/2021, Faculty of Medicine of Ain Shams University.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.
4. All the data of the patients and results of the study are confidential.
5. The researcher explains the aim of the study to the patient.
6. The patients have the right to withdraw from the study at any time.

**Sample size:** was calculated using PASS 11 for sample size calculation, setting the confidence level at 80% margin of error  $\pm$  0.15, and after reviewing previous study results according to Aaie, M study (2019). Our sample size was 30 patients.

**Inclusion criteria:** Our study included patients with OI whose age ranged from 3 to 16 years old. Patients were considered eligible for bisphosphonate treatment if they had long bone deformities with two or more low-trauma long bone fractures in two consecutive years or two or more vertebral compression fractures (at any time) and a height adjusted total body or lumbar spine BMD z-score less than -1.5 standard deviation (SD). A combination of one long bone and one vertebral fracture (**Oduah et al., 2017**).

**Exclusion criteria:** Patients with cardiac disease (e.g. coronary artery disease, aortic stenosis), EF less than 40%, previous MI. Uncontrolled hypertension. Respiratory impairment. Renal failure on hemodialysis. Bacteremia. Coagulopathy. Emergency surgery.

#### **Study Population:**

A cross-sectional study was conducted on 28 OI patients who

were recruited from the pediatric endocrinology unit at Ain Shams University during the period from October 2021 to October 2022. Echocardiography and pulmonary function tests of these patients were studied, at the time of recruitment, at the cardiology and pulmonology units respectively. Sixteen of the studied subjects had baseline echocardiography conducted before starting bisphosphonate therapy. The effect of bisphosphonate therapy on cardiac anatomy and functions was studied by comparing different echocardiographic parameters before and after 12 months of bisphosphonate therapy in the studied subjects.

### **Study Procedures:**

#### **All included children were subjected to the following:**

I. Full history from their caregivers including age, gender, socioeconomic standard, consanguinity of parents, history of cough, dyspnea, passive smoking, symptoms suggestive of OI including recurrent fracture deformities short stature, blue sclera, dentinogenesis imperfecta (Normal enamel with dentin abnormality), hearing impairment. Other features including increased joint laxity & mobility, short

stature, and easy bruising. Family history of the same condition.

II- Thoroughly clinical examination including: weight in kilograms (Kg), height in centimeters (cm), together with calculation of weight and height SDS (Tanner et al., 1966). Body mass index (BMI) together with calculation of BMI SDS according to the age and sex specific reference values (Cole, 2002).

III. Complete systemic examination (cardiovascular, respiratory, and neurological). Dental examination. Otologic examination for hearing loss. Complete neurological examination. Complications and comorbidities including; the presence or absence of vertebral fractures.

IV. ECHO study: Two dimensions echocardiography was performed on the patients in supine position or in left lateral semi-recumbency. Different views of the 2D echocardiogram and colour flow mapping were used. LV dimensions were measured by M-mode to get LV diameters (LVEDD and LVESD), intraventricular septal thickness (IVSD and IVSS) (cm), left ventricular posterior

wall thickness (LVPWD and LVPWS) (cm), ejection Fraction (Ej Fr), fractional shortening (FS%), and systolic function assessment by calculating the Ejection fraction using modified Simpson method. then, Follow up results of Echocardiography was compared to baseline data.

Dimensions were measured and reported in the form of z-score.

Aortic root diameter (AORD) (cm), ratio of the aortic annulus dimension to the left atrial dimension (AO/LA), intraventricular septal end diastole (IVSD) (cm), intraventricular septal end systole (IVSS) (cm), left ventricular internal dimension end diastole (LVIDD) (cm), left ventricular internal dimension end systole (LVIDS) (cm), left ventricular posterior wall thickness end diastole (LVPWED) (cm), left ventricular posterior wall thickness end systole (LVPWES) (cm), end diastolic volume (EDV) (ml), end systolic volume (ESV) (ml), ejection Fraction (Ej Fr), fractional shortening (FS %). Left ventricular external end diastolic diameter (LVEDD) (cm), posterior wall thickness

(PWT) (cm) and Left ventricular end systolic diameter (LVESD) (cm) were measured and reported in z-score.

VI- Pulmonary function tests were done by forced spirometry and impulse oscillometry (IOS). Pulmonary function tests with comment on forced expiratory volume in the first second (FEV1) %, forced vital capacity (FVC) %, FEV1/FVC, maximum expiratory flow (MEF) %, respiratory resistance (Rrs)%, frequency dependency of resistance (R20)% delta X, pattern of pulmonary function test (PFT) and area of reactance (Ax), pulmonary function test was performed on 26 patients only as 2 patients were young and uncooperative.

Lastly, active treatment was defined as Zoledronate dose 0.05 mg/kg every 6 months. Children less than 3 years of age received intravenous Zoledronate at a dose of 0.025 mg/kg per dose every 3 month. While children above 3 years old received 0.05 mg/kg/dose every 6 months with a maximum dose of 4 mg. Zoledronate was diluted in 50-100 ml 0.9% (normal saline) and given as intravenous infusion slowly over 30-45 min (**Trejo et al., 2016**).

Maintenance therapy was defined as Zoledronate dose 0.025 mg/kg 6monthly. The maintenance bisphosphonate therapy was initiated if the lumbar spine BMD Z score  $>-2$  SD, together with improvement in vertebral shape and the absence of any additional vertebral fractures.

If lumbar spine BMD- Z score  $>0$  SD, Zoledronate dose was reduced to 0.025 mg/kg every 12 months. The cumulative Zoledronate was expressed as milligrams per kilogram (Trejo et al., 2016).

Calcium and vitamin D intake was maintained according to the recommended daily allowance in all patients (Constantino et al., 2019).

### **Statistical Analysis:**

Data were collected, revised, coded and entered to the Statistical

Package for Social Science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two paired groups regarding quantitative data and parametric distribution was done by using Paired t-test while with non-parametric distribution was done by using Wilcoxon Rank test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at level of P-value  $< 0.05$ .

## RESULTS

Our results will be demonstrated in the following tables and figures:

**Table (1): Sociodemographic and baseline clinical characteristics of the studied group (N=28)**

		<b>Total (N=28)</b>
<b>Age (Years)</b>	Median (IQR)	9.90 (6.55-13.9)
<b>Gender</b>	Male	12 (42.9 %)
	Female	16 (57.1 %)
<b>Age at diagnosis (Years)</b>	Mean $\pm$ SD	1.1 $\pm$ 1.3
<b>Age at treatment onset of ttt. (Years)</b>	Mean $\pm$ SD	2.1 $\pm$ 0.8
<b>Duration of treatment (Years)</b>	Mean $\pm$ SD	6.0 $\pm$ 2.2
<b>Birth order</b>	1 <sup>st</sup>	5 (17.9 %)
	2 <sup>nd</sup>	8 (28.6 %)
	3 <sup>rd</sup>	13 (46.4 %)
	4 <sup>th</sup>	2 (7.1 %)
<b>Consanguinity</b>	No consanguinity	15 (53.6 %)
	First cousins	10 (35.7 %)
	Second cousins	3 (10.7 %)
<b>Similar condition in the family</b>	Yes	4 (14.3%)
	No	24 (85.7 %)
<b>Deaths due to similar condition in the family</b>	Yes	1 (3.6%)
	No	27 (96.4 %)
<b>Complaint</b>	Bone fracture	4 (14.3%)
	Bone deformity	24 (85.7 %)
<b>Easy bruising</b>		7 (25%)
<b>Blue sclera</b>		7 (25%)
<b>Dentinogenesis imperfecta (DI)</b>		11 (39.3 %)
<b>Hearing loss</b>		1 (3.6%)
<b>Bone tenderness</b>		5 (17.9%)
<b>Inguinal hernia</b>		2 (7.1%)
<b>Joint hypermobility</b>		2 (7.1%)
<b>Chest symptoms &amp; signs</b>	Normal	22 (78.5%)
	Pectus carinatum	5 (17.9%)
	Pectus excavatum	1 (3.6%)
<b>Abdominal symptoms &amp; signs</b>	Normal	28 (100%)

This table shows that the most common complaint was bone deformity (85.7%).

The age of our patients ranged from 3 to 16 years, with a

median (IQR) of 9.90 (6.55-13.9) years. The studied patients included 12 males (42.9%) and 16 females (57.1%).

**Table (2): Anthropometric parameters of the studied group (N=28)**

		Before ttt.	After ttt.	P-value
<b>Weight (kg)</b>	Median (IQR)	14 (9.9 – 18.3)	23.8 (14.8 – 34.8)	<0.001
<b>Weight SDS (SD)</b>	Mean ± SD	-4.3 ± 2.9	-2.8 ± 2.0	0.012
<b>Height (cm)</b>	Mean ± SD	93.7 ± 24.7	111.9 ± 21.6	<0.001
<b>Height SDS (SD)</b>	Mean ± SD	-4.3 ± 2.2	-4.5 ± 1.8	0.677
<b>BMI (kg/m<sup>2</sup>)</b>	Mean ± SD	15.9 ± 2.6	19.3 ± 4.5	0.001
<b>BMI SDS (SD)</b>	Mean ± SD	-0.8 ± 2.2	-0.5 ± 1.3	0.001
<b>Maternal height (cm)</b>	Mean ± SD	157.6 ± 4.6		
<b>Maternal height SDS (SD)</b>	Mean ± SD	-0.75 ± 0.76		
<b>Paternal height (cm)</b>	Mean ± SD	171.6 ± 6.5		
<b>Paternal height SDS (SD)</b>	Mean ± SD	-0.45 ± 0.98		
<b>Mid-parental height (cm)</b>	Mean ± SD	163.7 ± 6.0		
<b>Mid-parental height SDS (SD)</b>	Mean ± SD	-1.6 ± 0.93		
<b>TANNER staging (n=28)</b>	1	16 ((57.14%)		
	2	1 (3.5%)		
	3	3 (10.7%)		
	4	3 (10.7%)		
	5	5 (17.8%)		

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS)

•: Paired t-test & Wilcoxon Rank test

A significant increase between baseline and follow-up values of the patients' weight SDS and BMI SDS was noticed.

Meanwhile no significant difference between baseline and one-year follow-up values of the patients' height SDS.



**Table (3): Pulmonary function characteristics of the studied group (N=26)**

<b>FEV1% (n=25)</b>	Mean ± SD	100.9 ± 31.9
<b>FVC%</b>	Mean ± SD	89.7 ± 33.4
<b>FEV1/ FVC</b>	Mean ± SD	93.6 ± 10.5
<b>Comment</b>	Normal PFT	14 (53.8%)
	Restrictive PFT	10 (38.5%)
	Mixed	2 (7.7%)

Fourteen patients (53.8%) were normal, 10 patients (38.5%) had restrictive lung disease and 2 patients (7.7%) had mixed obstructive and restrictive patterns.

**Table (4): Comparison between Echo characteristics of the studied group at baseline and after treatment (N=16)**

		Baseline(n=16)	After ttt.(Follow up)	Test value	P-value	Sig.
AOR (cm)	Mean ± SD	1.93 ± 0.60	1.90 ± 0.45	0.571•	0.576	NS
AOR z-score	Median (IQR)	1.99 (1.16 – 3.1)	-1.4 (-1.65 – -1.25)	-3.351‡	0.001	HS
IVSd (cm)	Mean ± SD	0.73 ± 0.22	0.53 ± 0.13	-3.431•	0.008	HS
IVSd z-score	Median (IQR)	-2 (-2 – -2)	-0.33 (-0.93 – 0.39)	-2.803‡	0.005	HS
IVSd	Hypertrophy	0 (0.0%)	1 (3.6%)	0.367*	0.545	NS
IVSs (cm)	Mean ± SD	0.84 ± 0.09	0.87 ± 0.21	0.990•	0.348	NS
IVSs z-score	Median (IQR)	-2 (-2 – -2)	0.51 (-0.09 – 0.95)	-2.805‡	0.005	HS
IVSs	Hypertrophy	0 (0.0%)	3 (10.7%)	1.163*	0.281	NS
LVEDD (cm)	Mean ± SD	3.01 ± 0.70	4.05 ± 0.85	8.888•	0.000	HS
LVEDD z-score	Median (IQR)	-2 (-2 – -2)	1.14 (0 – 2.04)	-2.521‡	0.012	S
LVEDD	Dilated	0 (0.0%)	7 (25.0%)	2.483*	0.115	NS
LVESD (cm)	Mean ± SD	1.90 ± 0.50	2.41 ± 0.52	3.634•	0.008	HS
LVESD z-score	Median (IQR)	-2 (-2 – -2)	0.8 (-0.13 – 1.32)	-2.524‡	0.012	S
LVESD	Dilated	0 (0.0%)	4 (14.3%)	1.286*	0.257	NS
LVPWd (cm)	Mean ± SD	0.66 ± 0.16	0.58 ± 0.11	-1.481•	0.173	NS
LVPWd z-score	Median (IQR)	-2 (-2 – -2)	0.3 (-0.33 – 1)	-2.803‡	0.005	HS
LVPWd	Hypertrophy	0 (0.0%)	0 (0.0%)	0.000*	1.000	NS
LVPWs (cm)	Mean ± SD	1.02 ± 0.19	1.03 ± 0.33	0.116•	0.910	NS
LVPWs z-score	Median (IQR)	-2 (-2 – -2)	0.44 (-0.07 – 1.87)	-2.666‡	0.008	HS
LVPWs	Hypertrophy	0 (0.0%)	7 (25.0%)	3.065*	0.080	NS
AO/LA	Mean ± SD	1.13 ± 0.17	1.19 ± 0.23	0.912•	0.358	NS
EF (%)	Mean ± SD	66.98 ± 10.17	68.29 ± 4.46	0.721•	0.483	NS
FS (%)	Mean ± SD	35.20 ± 7.47	37.21 ± 3.55	1.706•	0.112	NS

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS)

\*:Chi-square test, Paired t-test & Wilcoxon Rank test

A significant decrease in the median AOR z-score and a significant increase in median z-scores of IVSd, IVSs, LVEDD, LVESD, LVPWd and LVPWs. Meanwhile, there was no

significant difference of mean EF, FS & AO/LA ratio before and after treatment. Two cases had impaired EF at baseline and after treatment EF became normal.

## DISCUSSION

In the current study, pulmonary function tests were evaluated in 26 patients using spirometry. About 10 patients (38.5%) had restrictive pulmonary disease and two had mixed pulmonary disease (7.7%). The restrictive pattern in OI disease can be explained by the presence of skeletal deformities in the chest wall and the spines (**Marom et al., 2020**). Multiple abnormalities of the lung connective tissue have been reported due to different causes. Respiratory complications in OI have been attributed to distal airspace enlargement associated with emphysema due to dysfunctional type I collagen, which results in a loss of pulmonary elastic recoil (**Baglole et al., 2018**). Lung defects in individuals with OI may be the primary result of abnormal collagen synthesis and not secondary to skeletal abnormalities (**Baldridge et al., 2010**).

Studies reported that increased aortic diameter is the most

common echocardiographic finding in OI patients type I (**Pinheiro et al., 2020**). The mean aortic z-score value of our patients at baseline was +1.99 (+1.16 to +3.1). Aortic root dilatation was reported in seven patients (46.7%) in the baseline study, which improved to -1.4 (-1.65 to -1.25) after one year of bisphosphonate treatment. **Price et al., (2001)** demonstrated the presence of a significant effect of bisphosphonate treatment on aortic root dilatation and aortic valve calcification. He proposed that bisphosphonates may prevent ectopic calcification of the aortic valve through inhibition of bone reabsorption, but also by exerting anti-inflammatory and lipid-lowering effects. Several trials showed the benefits of bisphosphonates on arterial and valvular calcification (**Elmariah et al., 2010; Innasimuthu, 2011**).

Intraventricular septal thickness at systole and diastole mean values were within normal ranges at baseline. During follow-up after bisphosphonate therapy,

the mean values of IVSd decreased with a statistically significant difference. However, one case showed increased IVSs and three cases had IVSd with no statistically significant difference to baseline. Many studies demonstrated that OI patients had higher mean values of IVS during systole and diastole than the control group **Pinheiro et al., (2020)** **Izui et al., (2022)**. The differences between variable studies could be referred to the disease severity. Variability in baseline values in left ventricular septal parameters could be attributed to the timing of echocardiographic evaluation during the disease course which means that some patients were evaluated early before developing cardiac problems.

In the present study, mean values of LVEDD and LVESD were within normal ranges at baseline. However, the mean values increased significantly during follow up. We had seven cases with dilated LVEDD and four cases with dilated LVESD. This could reflect that bisphosphonate therapy did not have a significant protective effect against LV dilatation. **Pinheiro et al., (2020)** reported higher LVEDD and LVESD diameter in OI patients in comparison to healthy controls.

Left ventricle changes can be attributed to greater myocardial tissue stiffness and decreased elasticity in OI patients leading to echocardiographic changes and altered myocardial relaxation (**Frommelt, 2006; Lamanna et al., 2013**). Bisphosphonates reduce the LV wall thickness. This is explained by inhibition of the activity of farnesyl pyrophosphate synthase which is a key regulatory enzyme in cell proliferation leading to increased wall elasticity (**Goncalves et al., 2015**).

The impaired LV function is a reflection of increased myocardial tissue stiffness. In the current study, a significant improvement in EF% & FS% was noticed in the studied cases after one year of bisphosphonates therapy in comparison to their baseline values. **Izui et al., (2022)** reported much higher mean values of EF among OI patients of type I and IV ( $84.2 \pm 4.9\%$ ,  $81.5 \pm 6.3\%$ ) in comparison to our patients. However, in type III the EF was lower. **Migliaccio et al. (2009)** found similar ejection fraction between patients with OI and healthy controls but reported that 95% of OI patients had diastolic dysfunction.

**Vouyouka et al., (2001)** attributed the occurrence of valve regurgitation to structural defects

in type I procollagen in OI patients. **Karamifar et al., (2013)** also reported that TR was the commonest valvular lesion in OI patients. Other survey studies concluded that AR and MR had higher incidence than TR in OI patients (**Najib et al., 2013; Vandersteen et al., 2014**).

In our study, valvular dysfunction was reported in five patients (17.9%) in the form of mild mitral regurgitation, trivial aortic regurgitation and mild tricuspid regurgitation. None of our cases had aortic stenosis.

### **CONCLUSIONS**

In conclusion, the commonest pulmonary disease in OI children was restrictive pattern and it was explained by the skeletal deformities in chest wall and spine. OI had variable pathologic effects on the heart. Some of these effects were reported in the baseline study as aortic root enlargement which affected 46.7% of patients, left atrial enlargement which was present in 60% of patients and impaired left ventricular ejection fraction which was diagnosed in two patients (14.3%). Otherwise, OI was not reported to have a significant effect apparently on intraventricular septum and left ventricular volumetric parameters in systole or diastole at baseline.

Bisphosphonates therapy had a significant effect on z- score of aortic root and ejection fraction, which improved significantly. However, treatment with bisphosphonates could not protect against the progressive effects of OI on cardiac muscle with time as the percentage of patients with impaired left ventricular volumetric parameters in systole or diastole increased significantly during follow-up.

### **RECOMMENDATION**

Further research is needed to increase our understanding of the effect of treatment with bisphosphonates on cardiac and pulmonary function in patients with osteogenesis imperfecta. It is now important to move forward into the area of prevention and to early detection for patients with osteogenesis imperfecta. Though it may be a challenge, future directions should be towards improving availability of both preventive and curative measures of osteogenesis imperfecta management to the general population. Further comparing different studies regarding different types of bisphosphonates, forms of administration, doses, and dose intervals in order to find the optimal treatment that interferes as little as possible with the patient's normal life and its effect on cardiac and pulmonary

function in patients with osteogenesis imperfecta.

### LIMITATIONS

The study had some limitations as being conducted on a small number of patients and not all patients were evaluated before starting therapy.

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