



## Alendronate ameliorates LS-BMD and BMD Z-score in $\beta$ -thalassemia major pediatric patients. A single-arm clinical study

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### General Note



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### ABSTRACT

**Introduction:** Osteoporosis associated with  $\beta$ -thalassemia major ( $\beta$ -Thal) has emerged as a significant problem due to increasing life expectancy in those patients. **Aim:** The aim of the current research was to evaluate the therapeutic effect of alendronate in  $\beta$ -Thal

children with either low or very low bone mineral density (BMD). *Methodology:* The study was carried out on 20  $\beta$ -thalassemic children (12 with very low BMD, Z-score < -2.5, and 8 with low BMD, Z-score -1.0–2.4) and 10 healthy children (control; Z-score > -1.0). BMD was assessed in all the study children (control, and before and after alendronate therapy) by dual-energy x-ray absorptiometry (DXA). *Results:* The findings of this research revealed that the BMD Z-score and BMD of the lumbar spine (LS-BMD) were significantly low in  $\beta$ -Thal children compared to the control children. Six months of alendronate therapy (10 mg daily) significantly improved BMD Z-score while non-significantly improved LS-BMD of  $\beta$ -Thal children compared to before treatment values. Besides, alendronate significantly improved the degree of osteoporosis in  $\beta$ -Thal children (6 very low BMD, 10 low BMD and 4 are normal BMD (Z-score > -1.0)). *Conclusion:* The current study recommends the use of alendronate for pediatric  $\beta$ -Thal patients with a BMD Z-score < -1.0.

**Keywords:**  $\beta$ -thalassemia, bone mineral density, alendronate, children

## 1. INTRODUCTION

Despite the marked improvement in the survival and life span of beta-thalassemia major ( $\beta$ -Thal) patients, osteoporosis remains a prevalent complication, even in well-iron chelated and well-transfused patients (Piga, 2017; Gaudio et al., 2019; Mehr et al. 2019). The pathogenesis of osteoporosis associated with  $\beta$ -Thal is attributed to many causes, including chronic anemia, iron toxicity, ineffective erythropoiesis, endocrine complications, and calcium, vitamin D, and zinc deficiency (Toumba and Skordis, 2010; Nakhakes et al., 2015). About 60 to 90% of  $\beta$ -Thal patients develop osteoporosis at a young age, which is associated with depressed bone formation and increased bone resorption (Morabito et al., 2004; Rossi et al., 2014).

Previous studies confirmed a decrease in bone mineral density (BMD), and a high incidence of osteoporosis among children of  $\beta$ -Thal. Therefore, these children must be diagnosed and managed with appropriate osteoporosis treatment (Ishaq et al., 2015; Meena et al., 2015). The Dual-energy x-ray absorptiometry (DXA) is currently the most reliable and widely used technique to measure BMD, which classically assesses BMD at the proximal femur and lumbar spine (Garg and Kharb, 2013; Choi, 2016). Recently, Ward et al. (Ward et al., 2016) reported that a BMD Z-score of  $\leq -2$  SD diagnoses a child with osteoporosis.

Bisphosphonates (Bis), synthetic analogs of pyrophosphate, are inhibitors of bone resorption and turnover. They also increase BMD and hence improve the structure and composition of bone (Drake et al., 2008; Lewiecki, 2010). The increased bone resorption observed in  $\beta$ -Thal patients has specified the indication of Bis in the treatment of Thal-associated osteoporosis (Gaudio et al., 2008). In adults, Bis are widely used for protecting and cure osteoporosis associated with Thal (Forni et al., 2012; Giusti, 2014). On the other hand, there are not enough long-term efficacy and safety studies for Bis treatment in children and adolescents, However, Bis are still the most extensively published agents for the treatment of osteoporosis in pediatrics (Baroncelli and Bertelloni, 2014; Bhatt et al., 2014).

Alendronate is a Bis derivative that contains nitrogen in its R side chain. It is a potent inhibitor of osteoclast function and activity where it diminishes bone turnover via promoting osteoclast apoptosis. Besides, it increases BMD (Drake et al., 2008; Gaudio et al., 2008). The current research aimed to investigate the potential therapeutic impact of alendronate on BMD in  $\beta$ -Thal children diagnosed with low and very low BMD. DXA will be performed to assess BMD in the children under the study.

## 2. METHODOLOGY

### The population of the study

Thirty children aged 8-14 years, 20 of them are  $\beta$ -Thal patients, and ten are healthy children served as a control group joined this research. The  $\beta$ -Thal children were collected from the Outpatients Pediatric Hematology/Oncology Unit, Tanta University Hospital, Tanta, Egypt, over 12 months duration (May 2017 - May 2018). 70% of the  $\beta$ -Thal children had a positive family history for the disease, 60% regularly administered desferal, 45% suffered from hepatosplenomegaly, and 55% had a splenectomy.

### Inclusion criteria

For the control children: normal BMD (Z-score > -1.0). For  $\beta$ -Thal children: homozygous  $\beta$ -Thal, BMD Z-score < -1.0 (12 with very low BMD, Z-score < -2.5, and 8 with low BMD, Z-score -1.0–2.4) (Fig. 1). The BMD Z-score was assessed by DXA. Informed consent from the parents or the guardians of the 30 children was assigned. The protocol of the study was approved by ethical committee Tanta University, Egypt. Any unexplained risk was notified to the ethical committee and parents.

### Exclusion criteria

Children with malnutrition, endocrine diseases, hormone replacement therapy, renal, and stomach disease. The presence of scoliosis, vertebral deformity, and fractures. Medications that may influence bone formation and resorption such as steroids, vitamin D and calcium.

### Assessment of serum ferritin

Serum ferritin and CBC were assessed in El-Safwa Laboratory, Tanta, Egypt.

### Alendronate therapy

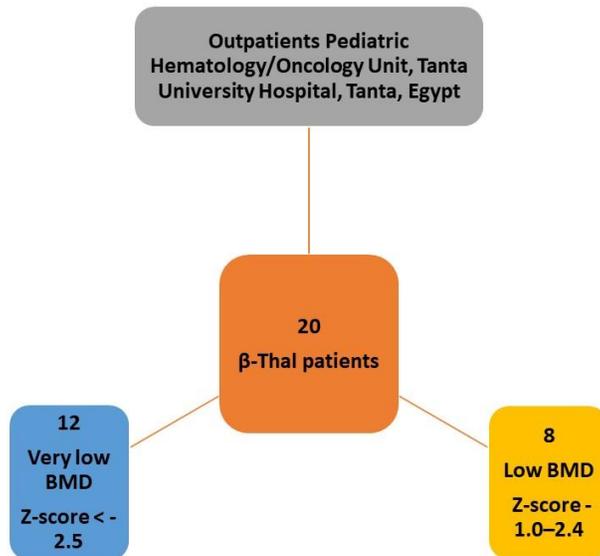
Alendronate 10 mg tablet (Bonapex©, Apex Pharma, Bangladesh) once daily was administered to  $\beta$ -Thal children for six months.

### Assessment of BMD

This assessment was done on an outpatient basis, at baseline, and after six months of alendronate therapy. The Hologic DXA system osteodensitometer assessed the absolute lumbar spines (LS) -BMD. DXA scan results were expressed as Z-scores, which were calculated according to bone density values using sex and age-matched healthy population. BMD Z-scores from -1.0 up to -2.5 SD were defined as low BMD (osteopenia), BMD Z-scores below -2.5 SD were described as very low BMD (osteoporosis), and BMD Z-scores above -1.0 SD were defined as normal BMD (Doulgeraki et al., 2012).

### Statistical analysis

Results were presented as the mean  $\pm$  SD. All statistical analysis was carried out according to the treatment method using GraphPad Prism Version 5. A comparison of baseline clinical characteristics between  $\beta$ -Thal and the control was performed using either the chi-square ( $X^2$ ) test or the unpaired student t-test. A comparison between results before and after alendronate therapy was performed using the paired student t-test. p values < 0.05 were considered statistically significant.



**Figure 1.** Patients inclusion criteria flow chart

## 3. RESULTS

### Baseline clinical characteristics of the study population

There were no significant differences regarding age, sex, weight, and height among  $\beta$ -Thal and the control children.  $\beta$ -Thal patients showed significantly higher ferritin (93%,  $p = 0.001$ ) compared to the control value. On the other hand,  $\beta$ -Thal patients displayed a significant decrease in the body mass index (BMI) (15%,  $p = 0.024$ ), absolute LS-BMD (27%,  $p < 0.001$ ) and BMD Z-Score (35%,  $p < 0.001$ ) compared to the control children values (Table 1).

**Table 1** Clinical features of 20 beta-thalassemia major ( $\beta$ -Thal) children and 10 healthy children (control).

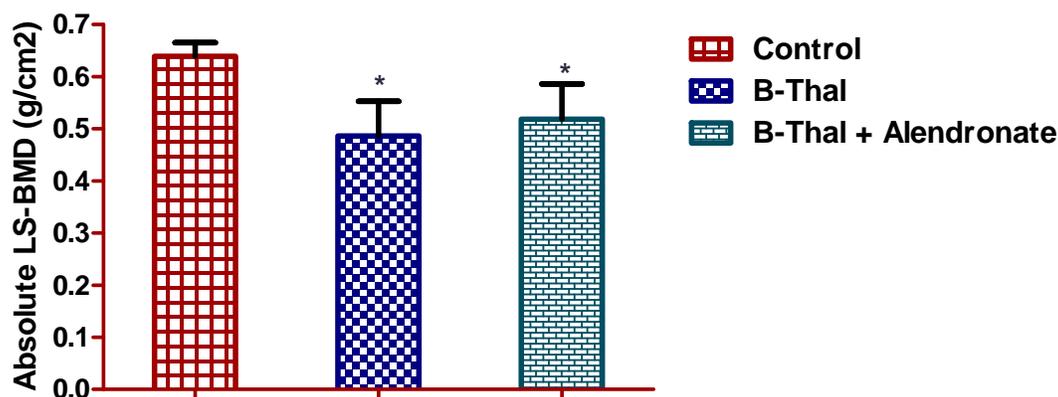
Characteristics	$\beta$ -Thal (n = 20)	Control (n = 10)	p-value
Age (year)	10.475 $\pm$ 2.34	11.15 $\pm$ 2.07	0.446
Sex, n (%)	11 males	4 males	0.439
	9 females	6 females	
Weight (kg)	27.90 $\pm$ 7.81	29.40 $\pm$ 8.48	0.633
Height (cm)	134.10 $\pm$ 9.91	138.80 $\pm$ 12.99	0.279
BMI (kg/m <sup>2</sup> )	15.31 $\pm$ 2.73 <sup>a</sup>	18.09 $\pm$ 3.56	< 0.05
Ferritin (ng/ml)	1554 $\pm$ 991 <sup>a</sup>	102 $\pm$ 24	< 0.001
Absolute LS-BMD (g/cm <sup>2</sup> )	0.47 $\pm$ 0.06 <sup>a</sup>	0.64 $\pm$ 0.03	< 0.001
BMD Z-Score	-2.92 $\pm$ 0.55 <sup>a</sup>	-0.64 $\pm$ 0.184	< 0.001

Results expressed in mean  $\pm$  SD, number (n) and percentage (%). <sup>a</sup> Significantly different from the control group.

Abbreviations: BMI – body mass index; LS-BMD – lumber spine bone mineral density, BMD Z-Score – bone mineral density Z-Score

### Effect of alendronate treatment on absolute LS-BMD examined in $\beta$ -Thal children

Treatments of  $\beta$ -Thal children with 10 mg alendronate daily for 6 months resulted in a nonsignificant increase (7%,  $p = 0.5924$ ) in the absolute LS-BMD value compared to the before alendronate value (Figure 1). Furthermore, treatments of  $\beta$ -Thal children with alendronate still presented a significantly lowered LS-BMD value (19%,  $p < 0.05$ ) compared to the control value (Fig. 2).

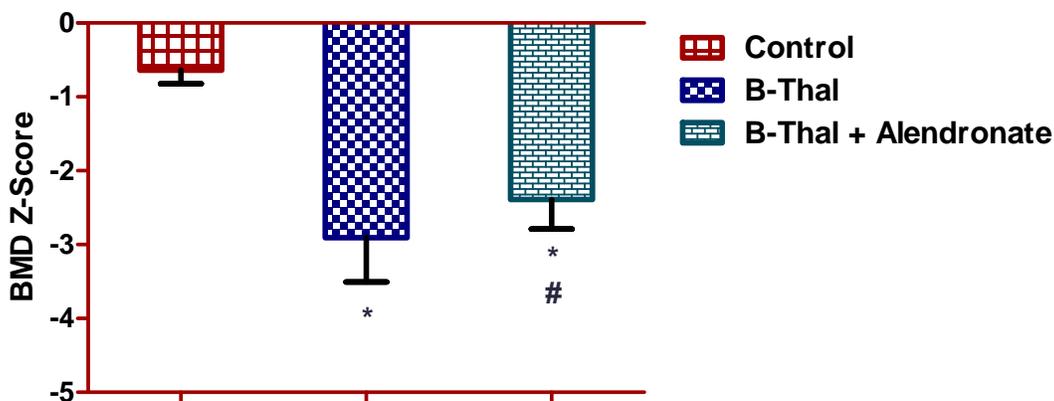


**Figure 2.** Comparison of absolute lumber spine-bone mineral density (LS-BMD) values of 10 healthy children (control) and 20 beta-thalassemia major children ( $\beta$ -Thal) before and after 6 months of alendronate therapy. Results were offered as mean  $\pm$  SD. <sup>a</sup>Significantly different from the control group.  $p$  values < 0.05 were considered statistically significant.

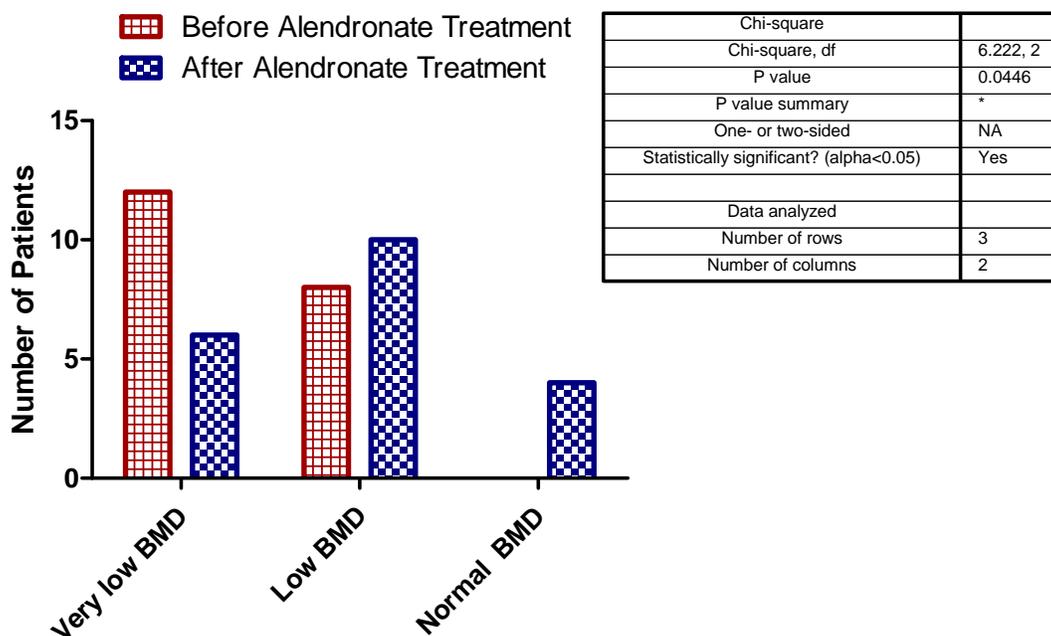
### Effect of alendronate treatment on BMD Z-score examined in $\beta$ -Thal children

Treatments of  $\beta$ -Thal children with 10 mg alendronate daily for 6 months caused a significant increase (22%,  $p < 0.05$ ) in BMD Z-score compared to before alendronate value. Besides, alendronate treated  $\beta$ -Thal children still showed a significantly lower BMD Z-score ( $p < 0.05$ ) compared to the control group value (Fig. 3).

Furthermore, 60 % of the  $\beta$ -Thal children involved in the present study showed very low BMD (BMD Z-score < -2.5), and 40% showed low BMD (BMD Z-score from -1.0 up to -2.4). Fortunately, after treatment with alendronate, only 30% of  $\beta$ -Thal children showed very low BMD, 50% showed low BMD, and 20% showed normal BMD (BMD Z-score > -1.0). The chi-square analysis showed a significant difference between all categories ( $p < 0.05$ ) (Fig. 4).



**Figure 3.** Comparison of bone mineral density (BMD) Z-Score values of 10 healthy children (control) and 20 beta-thalassemia major children ( $\beta$ -Thal) before and after 6 months of alendronate therapy. Results were offered as mean  $\pm$  SD. \*Significantly different from the control group. # Significantly different from  $\beta$ -Thal before the alendronate group. p values  $< 0.05$  were considered statistically significant.



**Figure 4.** A bar chart represents the distribution of 20 beta-thalassemia major ( $\beta$ -Thal) patients according to BMD Z-Score before and after 6 months of alendronate therapy. Chi-square analysis showed a significant difference after treatment ( $p < 0.05$ ).

#### 4. DISCUSSION

The present research aimed at investigating the impact of alendronate therapy for six months on bone health in  $\beta$ -Thal pediatric patients. Twenty  $\beta$ -Thal children all with bone complications were enrolled in the present study. According to the DXA scan, eight (40%) of the study patients showed low BMD (osteopenia), and 12 (50%) showed very low BMD (osteoporosis). All (100%) control children showed normal BMD measurements. At the beginning of the research, DXA scans results showed that both LS-BMD and BMD Z-score are significantly lower in  $\beta$ -Thal patients compared to the control group. Six months of alendronate therapy significantly improved both the degree of osteoporosis in  $\beta$ -Thal children (6 very low BMD, ten low BMD, and 4 are normal BMD) and BMD Z-Score. Unfortunately, there was no improvement noticed regarding LS-BMD in  $\beta$ -Thal patients after alendronate therapy.

Terpos and Voskaridou (2010) demonstrated that Thal-associated osteoporosis might result from multiple causes, including hypothyroidism, the presence of diabetes, delay in sexual maturation, , progressive marrow expansion, iron toxicity on osteoblasts, iron chelators, deficiency of the growth hormone and insulin growth factors.

Several studies reported that alendronate therapy improved LS-BMD in Thal patients. However, in the majority of these studies', alendronate was administered for a more extended period (2 years) while in our study, alendronate was administered only for six months. Leung et al. (2009) showed that two years of alendronate therapy improved LS-BMD in 62% of Thal children compared to calcium and vitamin D treatment. Moreover, Morabito et al. (2004) demonstrated that alendronate therapy to 25 Thal adolescents for two years significantly decreased pyridinium crosslinks (bone resorption marker) while significantly increased LS-BMD. Voskaridou and Terpos (2008) studied 66 Thal patients with osteoporosis and demonstrated that six months of alendronate therapy effectively increased BMD and reduced bone resorption.

Bis successfully decreases osteoclast activity in the resorptive phase of bone remodeling and protects bone micro-architecture, both significant determinants of bone strength and, eventually, the vulnerability to fractures. The unique chemical structure of each Bis used in the treatment regulates its specific affinity, distribution/diffusion all over the bone, and its impacts on bone geometry, micro-architecture, and structure or what is known as 'bone quality' (Miki and Naka 2005).

## 5. CONCLUSION

In conclusion, the results of this study showed that alendronate might exert a positive impact on the bone state in pediatric  $\beta$ -Thal patients and BMD Z-Score. Besides, this study indicates that Bis remains an essential treatment option for osteoporosis associated with Thal. The study recommends the use of alendronate (10 mg tablet once daily) for pediatric  $\beta$ -Thal patients with a BMD Z-score < -1.0. Further studies with larger sample size and a prolonged alendronate therapy duration are advised.

### List of Abbreviations

$\beta$ -Thal:  $\beta$ -Thalassemia major; BMD: Bone mineral density; DXA: Dual-energy x-ray absorptiometry; LS-BMD: Lumbar spine- BMD; Bis: Bisphosphonates; BMI: Body mass index.

### Author Contributions

El-Shanshory MR: Conceptualization; Shaat AA: Methodology; Erfan AA and El Badry AMT: Investigation, El-Shitany NA: Writing—original draft preparation; Binmahfouz LS and El-Shitany NA: Review & editing.

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### Conflict of Interest

The authors declare no conflict of interest.

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### Data and materials availability

All data associated with this study are present in the paper.

### Peer-review

External peer-review was done through double-blind method.

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