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Research Article

Assessment of the Admission and Follow-up Characteristics of Children Diagnosed with Secondary Osteoporosis

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What is known about this topic?
Secondary osteoporosis is a condition when the underlying disease or its treatment causes the bone mass to decrease and the bone structure to deteriorate, increasing the risk of fracture. The importance of diagnosis and treatment during childhood and adolescence is due to its long-term negative effects.

What does this study add?
Secondary osteoporosis is common in children, mostly in chronic inflammatory diseases.Vertebral involvement is common in patients with secondary osteoporosis, even in the absence of a history of significant fracture at the time of diagnosis. The efficacy of bisphosphonate therapy has been demonstrated in patients with secondary osteoporosis with and without a history of steroid drug use.

ABSTRACT
Objective: Secondary osteoporosis is a condition when the underlying disease or its treatment causes the bone mass to decrease and the bone structure to deteriorate, increasing the risk of fracture. The importance of diagnosis and treatment during childhood and adolescence is due to its long-term negative effects. In this study, our objectives were to determine the diagnostic findings, treatment efficacy, and follow-up characteristics of childhood with secondary osteoporosis.
Methods: 61 patients diagnosed with secondary osteoporosis between January 2000 and January 2021 were included in the study. The research is a cross-sectional and descriptive study. Study participants had to be under 18 years of age when the primary underlying disease was diagnosed and received treatment for secondary osteoporosis. Patient data were collected from patient files. Patient data were obtained from patient files in hospitals and were interpreted through the IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY, USA).
Results: 61 patients (28 women/33 men) were evaluated. The most common underlying primary diseases in patients with secondary osteoporosis were inflammatory diseases (57.7%), neuromuscular diseases (26.2%), immunodeficiency (13.1%), acute lymphoblastic leukemia (8.2%), metabolic diseases (8.2%), and solid organ transplantation. (8.2%), bone marrow transplantation (6.6%) and epilepsy (6.6%). The average chronological age when secondary osteoporosis was diagnosed was 11.89±4.88 years. They were evaluated for osteoporosis 6.39±5.13 years after the onset of the underlying primary chronic diseases. 78.7% of the patients had one or more chronic drug use. Systemic steroid use was 59%, chemotherapeutics 23%, immunomodulatory drugs 19.7%, antiepileptic drugs 8.2%, inhaled steroids 4.9%, IVIG 1.6%, and antituberculosis drugs 1.6%. Additionally, 1.6% of the patients were using testosterone as replacement, 3.3% L-Thyroxine, 1.6% estrogen, and 1.6% growth hormone. Bone pain was detected in 49.2% of the patients. All patients had vertebral fractures before treatment. Bisphosphonate treatment was given to 45 patients with secondary osteoporosis. There was a statistically significant increase in mean bone mineral density (BMD) and bone mineral content values six months after treatment, ($p<0.001$). There was a significant increase in BMD Z-score values for chronological and height age ($p<0.001$). The patients' BMD values increased on average by 31.15% with treatment. Following bisphosphonate treatment, there was a significant reduction in both fracture number and bone pain in patients ($p<0.01$). When patients who received and did not receive steroid treatment were compared, both groups received similar benefits from bisphosphonate treatment.
Conclusion: Secondary osteoporosis is a condition that is influenced by many factors, such as the primary disease causing osteoporosis, chronic medication use, especially steroids. If left untreated, osteoporosis leads to important diseases such as bone pain, bone fractures, immobilization, and reduced linear growth of bone. When used to treat childhood secondary osteoporosis, Bisphosphonates significantly improve BMD and reduce fracture risk.
Keywords: Childhood, secondary osteoporosis, BMD, treatment, bisphosphonate

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INTRODUCTION

A higher risk of fracture defines osteoporosis due to a reduction in bone mass and degradation of the microarchitecture of the bone (1). A significant amount of bone mass is reached during childhood and adolescence. Therefore, childhood is a significant period for bone health for the development of a strong musculoskeletal system. To prevent long-term deformities, maintain bone health and improve quality of life, it is critical to identify, diagnose, treat, and manage individuals at risk of developing osteoporosis in this period (2).
When one or more vertebral fractures occur without the presence of high-energy trauma, local disease, or a history of severe fractures with low bone density, it is considered osteoporosis in children and adolescents (3). Osteoporosis can be divided into primary and secondary osteoporosis. Primary osteoporosis is caused by intrinsic skeletal problems such as abnormalities in collagen tissue, bone production, or mineralization. It can also be inherited. Otherwise, chronic drug usage or the underlying primary diseases can cause secondary osteoporosis. Diseases causing secondary osteoporosis in children can be grouped as neuromuscular diseases, endocrine disorders, metabolic diseases, chronic inflammatory diseases, and iatrogenic(4).

Often, the focus on the underlying primary disease and its treatment can lead to bone health being overlooked. Deterioration of bone health leads to fractures and immobilization and makes managing the patient difficult. Some patients may be evaluated for osteoporosis only when a fracture develops (5).

In the treatment of osteoporosis, determination and treatment for the underlying causes are gaining importance treatment aims to reduce bone pain, increase bone mass, reduce the risk of fractures, and increase patient's mobility. For this purpose, bisphosphonates, which are synthetic pyrophosphate analogs that bind to osteoclasts, inhibit their action, and increase osteoclast apoptosis, are frequently used in treatment. There is limited information and studies on the dosage and duration of use of bisphosphonates in children, especially in secondary osteoporosis (6).

In this study, we aimed to determine the diagnostic findings of childhood secondary osteoporosis, to reveal morbidities such as fractures and immobilization, to reveal follow-up characteristics, and to determine the efficacy of bisphosphonate treatments. This study also emphasizes that clinicians should evaluate the patient for osteoporosis according to risk factors during chronic disease follow-up.

METHODS

A total of 61 patients diagnosed with secondary osteoporosis between January 2000 and January 2021 were included in the study. The study was cross-sectional and descriptive. The study was approved by the Ethics Committee of Ankara University (Approval number: İ7-441-20). The underlying disease was defined as "primary disease".

Inclusion criteria:

- Age <18 years at diagnosis of primary disease, currently being followed up in our clinic,
- Presence of one or more vertebral fractures in the absence of local disease or high-energy trauma,
- Bone mineral density (BMD) Z-score ≤ -2.0 on Dual Energy X-ray Absorptiometry (DEXA) measurements; 2 or more long bone fractures by age ten years; 3 or more long bone fractures by age 19 years,
-Conditions that carry a risk of osteoporosis: chronic systemic inflammatory diseases, using drugs such as steroids that affect bone, diseases that cause immobilization (neuromuscular diseases, etc.), several diseases that may affect bone metabolism (hormonal deficiencies, anorexia neurosis, etc.)

Patients with BMD Z-score above -2 and long bone fractures, patients with BMD Z-score above -2 and no vertebral fractures, patients without chronic systemic disease and/or drug use, and those with genetic or clinical diagnosis of primary osteoporosis were excluded.

Patient data were obtained from hospital patient files. Demographic data, underlying primary diseases and their characteristics, duration of immobilization, if any, chronic drug use, coexistence of additional endocrine diseases, presence and duration of bone pain, bone fracture characteristics and nutritional status were examined. Patients were followed up regularly every 6 months. During physical examination, anthropometric characteristics and pubertal stages of the patients were evaluated. In anthropometric evaluation, body weight (BW), height, height SDS, body mass index (BMI), and BMI% were recorded and evaluated according to national reference data (7).

Bone metabolism markers (serum calcium (Ca), phosphorus (P), parathormone (PTH), 25 hydroxy vitamin D (25(OH)D), urinary calcium excretion, and additional biochemical measurements, if any, were analyzed in the pre-and post-treatment laboratory data of patients. Vitamin D deficiency was diagnosed with a serum 25(OH)D level below 20 ng/mL (8).

DEXA (Hologic Explorer®) was used to measure lumbar 1-4 vertebrae BMD. BMD, bone mineral content (BMC), bone surface area, and Z-score were calculated according to normal reference values (9). Lateral vertebral radiographs were examined by pediatric radiologists and pediatric endocrinologists. Vertebral fractures were evaluated according to the Genant Classification (10).

Patients were treated with bisphosphonate therapy, such as pamidronate, zolendronic acid, or alendronate. DEXA measurements were performed before treatment, at the 6th month of treatment and during the follow-up period. The last measurements of BMD were also recorded. Characteristics of bisphosphonate treatment dose and duration were analyzed.

Different bisphosphonate options were determined according to current approaches to osteoporosis treatment, drug availability, and the patient's treatment preference. Pamidronate was administered at a dose of 1 mg/kg/day intravenously on three consecutive days and repeated every three months. Zoledronic acid was administered intravenously at a dose of 0.05 mg/kg/ every six months and alendronate orally at a dose of 70 mg/week. Calcium supplementation was given for 14 days following treatment. Oral elemental calcium 25-50 mg/kg/day was given. The dose was adjusted according to blood calcium level. Patients with vitamin D deficiency were given D3 at a treatment dose of 2000 IU/day for at least 6 weeks. Maintenance treatment was given at a dose of 400-1000 IU/day depending on the blood 25OHD3 levels (8).

IBM SPSS Statistics 20 program was used for statistical analysis. Statistical $p < 0.05$ was accepted as the significance limit. Mean, standard deviation, median, minimum, maximum, minimum, and maximum values were given in descriptive statistics for continuous data, and number and percentage values were given in discrete data. Shapiro-Wilk test was used to examine the conformity of the data to normal distribution. In comparing pre- and post-treatment laboratory values, BMD, BMI, and BMD Z-score values, the paired samples t test was used for the data conforming to normal distribution and the Wilcoxon test was used for the data not showing normal distribution. The McNemar test was used for pre-treatment and post-treatment comparisons of nominal variables. Chi-Square and Fisher's Exact test were used for group comparisons of nominal variables (in cross-tabulations).

RESULTS

The study included 61 patients (28 female/33 male). The most common underlying primary disease in patients with secondary osteoporosis was chronic inflammatory diseases (57.7%) (Table 1).

The mean chronological age at the time of secondary osteoporosis diagnosis was 11.89±4.88 years. They were evaluated for osteoporosis 6.39±5.13 years after the onset of underlying primary chronic diseases. The mean height SDS was -1.78±2.19. Twenty-three patients (37.7%) had a height SDS below -2 SD and had short stature at the time of diagnosis. At the time of diagnosis, 54.1% of the patients were prepubertal (Table 2).

One or more chronic drug use was present in 78.7% of the patients. Systemic steroid use was 59%, chemotherapeutics 23%, immunomodulatory agents 19.7%, antiepileptic drugs 8.2%, inhaled steroids 4.9%, IVIG 1.6%, and antituberculosis drugs 1.6%. In addition, 1.6% of the patients were using testosterone, 3.3% L-Tyroxine, 1.6% estrogen, and 1.6% growth hormone as a replacement.

Bone pain was detected 49.2% of patients. Of these, 37.7% had low back pain. All patients had vertebral fractures before treatment (n:61). Femur was the most commonly fractured long bone (7.9%). Non-traumatic long bone fractures were present in 12.8% of the patients. Before endocrinological evaluation, the number of long bone fractures per year was 1 in 15.8% and 2 in 7.9% of cases.

The average BMD Z-score of the cases included in the study was 0.47±0.16 g/cm2, and the BMD Z-score according to chronological age was -3.62±1.16. Total BMC was 19.76± 10.51 g, and the average BMD Z-score for height and age was -2.77±1.63.

When the 25OHD3 levels of the cases were evaluated at the time of secondary osteoporosis diagnosis, it was determined that the serum vitamin D level of 30 cases (%49,1) was below 20 ng/ml, and then vitamin D replacement was applied. There were still 17 cases (%27,8) with serum vitamin D levels below 20 mg/ml at the 6th-month follow-up of bisphosphonate treatment despite vitamin D replacement.

Of the 61 patients, 45 (73%) received bisphosphonate treatment (an additional 2 patients were referred to a different center for treatment). Sixteen patients who were diagnosed with secondary osteoporosis but did not attend follow-up or did not have regular follow-ups did not receive treatment.

Patients received biphosphonate such as zolendronic acid, pamidronate, or alendronate. The minimum duration of bisphosphonate treatment was 6 months and maximum 4 years (mean 1.2 years). Thirty-one patients (71%) received zoledronic acid treatment with the mean duration of 0.83±0.45 years. Alendronate treatment was administered to five patients (11.6%) for an average of 1.00±0.61 years. Ten patients (23.3%)

received pamidronate treatment. The mean duration of pamidronate treatment was 1.65±1.08 years. One patient received alendronate and then pamidronate. Also, two patients received pamidronate and then zoledronic acid.
With bisphosphonate treatment, there was an increase of 0.111±0.09 gr/cm2 in the mean total BMD after six months of treatment ($p<0.001$). Also, BMD Z-scores values increased 6 months after treatment ($p<0.001$) (Figure 1). There was no difference between the mean area of L1-L4 vertebrae before and after treatment ($p>0.05$) (Table 3).
When the total BMD values of the patients before and after the last bisphosphonate treatment (mean treatment duration was 1.10±0.89 year) were compared, an increase of 0.169±0.0.116 gr/cm2 was found ($p<0.001$). A mean increase of 31.15±30.48% was seen in the BMD values after six months of biphosphonate treatment compared to before treatment.
There was no statistically significant difference between the height SDS, BMI and BMI% of patients with secondary osteoporosis who received treatment before and 6 months after treatment ($p>0.05$) (Table 3). Pubertal progression was observed in 8 patients.
There was a difference between bone pain and fracture rates in patients with secondary osteoporosis before and after treatment ($p<0.001$). Of 20 of 27 patients with bone pain before treatment, the pain dissolved after treatment. In 14 of 43 patients (32.5%) who had fractures before treatment, no fracture was detected after treatment ($p<0.05$). Only 1 of 32 patients without fracture had nontraumatic fracture after treatment. No patients had long bone fractures after treatment.
Thoracic and lumbar vertebra involvement significantly improved with treatment ($p<0.01$). Of 26 patients with thoracic vertebrae pathology, improvement were seen in 11 (42.3%) patients with bisphosphonate treatment. Improvement in vertebral morphology was seen in all cases with lumbar vertebra involvement (N:19,61.3%) (Increase in vertebral BMD and height, reshaping of vertebral fractures).There was no difference in the presence of scoliosis before and after treatment ($p>0.05$).
Serum Ca, P, ALP, vitamin D, and PTH levels did not differ between before and after biphosphonates ($p>0.05$) (Table 3).
Cases using steroids and cases without steroid use were compared in terms of their response to bisphosphonate treatment (Table 4). There was an increase of 0.114±0.086 g/cm2 in the mean total BMD after the first 6th months of bisphosphonate treatment in patients with chronic steroid use ($p<0.001$). An additional 0.05±0.118 g/cm2 increase of BMD ($p<0.05$) was seen between the 6th months of treatment and the last examination. Similar increment of BMD were seen in other patients which were not given steroid treatment (0.087±0.052 g/cm2 in first 6th monhs, 0,053±0.086 g/cm2 between 6th months to last examination) ($p<0.001$). There was no statistically significant difference ($p>0.05$) between the percent change in total BMD values of steroid users and other chronic drug users (Table 5).
In only one case (2.3%), side effects were noted during bisphosphonate treatment. In this case, fever was recorded as an adverse effect approximately 2 hours after intravenous Zoledronic acid infusion.

Study Limitations

The limitation of our study was the relatively short follow-up period in our patients treated for osteoporosis does not yet-term follow-up of these patients is planned. Another limitation of our study is that there is no consensus or treatment guide in the literature for the treatment of secondary osteoporosis in children.

DISCUSSION

In this study, we evaluated the diagnostic features and response to bisphosphonate therapy in a large group of children and adolescents with secondary osteoporosis. The most common underlying primary disease in patients with secondary osteoporosis was chronic inflammatory diseases. Chronic medications,most frequently steroids, were used in most of the patients.
The mean age of patients diagnosed with osteoporosis was 11.89 years. Similar ages were reported in the literature. In a study by Inoue et al. 39 patients with secondary osteoporosis were analyzed and the mean age at diagnosis of secondary osteoporosis was found as 12 years. Zacharin et al.reported that the mean age at diagnosis of secondary osteoporosis was found to be 10.1 years in their series of Duchenne muscular dystrophy (11,12).
Almost one-third of our cases had short stature at the time of diagnosis. The duration and severity of chronic systemic diseases and the use of drugs that affect growth, especially steroids, are factors that cause growth retardation. As it is known, DEXA measurements give areal measurement results, not volumetric in bone. It measures a three-dimensional object in two dimensions spatially, and bone size affects the measurement result. So, they may give lower measurement results in short children than in children of normal height of the same age (13). For this reason, we would like to emphasize that it should be determined whether there is short stature in cases with chronic diseases and that evaluations should be made considering this situation.
Since the primary diseases examined in our study and in the literature differ between centers, the age at diagnosis and the duration of development of osteoporosis after the primary disease may differ (14,15). Among the factors affecting this situation, there are many variables such as the geography where the centers are located, the population, and the clinical experience of the center (16,17). However, cases with secondary osteoporosis were referred to our pediatric endocrinology department for evaluation a long time after the diagnosis of their primary disease (6.39±5.13 years after the onset of their disease). This makes us think there may be little awareness that bone health can be affected during various primary diseases, and secondary osteoporosis may be diagnosed late.
The fact that the average age of first fracture in the cases was 6.63±4.31 years actually emphasizes the delay in diagnosing osteoporosis despite the early fracture. Evaluation of osteoporosis in patients with chronic diseases before fractures develop is important in terms of morbidity. Another valuable finding of our study is that all our patients had vertebral fractures. Focusing on the treatment of chronic primary disease and considering osteoporosis only in long bone fractures delays the diagnosis in patients with secondary osteoporosis.In chronic patients, conditions that negatively affect bone density such as immobilization, steroid-antiepileptic drug use should be questioned and lateral vertebral radiography should be performed even in the absence of long bone fracture in terms of osteoporosis. We clearly recommend that clinicians who follow chronically ill patients should evaluate them for osteoporosis with lateral vertebral radiography.
Our study's most common primary disease was chronic inflammatory diseases, followed by neuromuscular diseases. Factors such as increased osteoclastic activity as a result of increased cytokines in chronic inflammatory diseases, disruption of the mechanostat mechanism in neuromuscular diseases, increased immobilization, steroids used in their treatment, anticonvulsant treatment and malnutrition lead to the development of secondary osteoporosis (1,12). Clinicians should not neglect careful evaluation in terms of bone health especially in the follow-up of this group of diseases.
In addition to the primary disease, several drugs also play a role in the development of osteoporosis. Most of the patients were on one or more chronic medications. Long-term steroid use is required in the treatment of these diseases and 63.9% of our patients had systemic and inhaled steroid use. The characteristics of the cases with secondary osteoporosis in our study and in the literature may show differences as well as similarities. This is since factors such as the heterogeneity of the patients' primary diseases, the characteristics of the patient groups included in the study, the nature of the drugs they use, and the different duration of drug use affect the results of the studies (18,19).
Additionally, vitamin D deficiency was detected in a significant number of our cases. Although replacement was given in cases with deficiency, vitamin D was still low in 17 cases at the end of the 6-month follow-up. Optimal levels of vitamin D are crucial in maintaining bone health (20). Focusing on underlying problems may lead to neglect of checking vitamin D levels and treating the deficiency, if any. Care should be taken to bring vitamin D levels to normal limits in chronic patients, which may have negative effects on bone health. In patients with secondary osteoporosis, treatment of the etiology, if possible, will stop the negative effect on bone metabolism. If etiologic factors persist, it would be appropriate to evaluate bone health, eliminate vitamin D deficiency, continue long-term follow-up of patients with osteoporosis, and give osteoporosis treatments.

There is no consensus or treatment guideline in the literature for the treatment of secondary osteoporosis in children. In our study, bisphosphonate treatment was administered to 45 patients in our clinic. In the expert panel consensus recommendations for the diagnosis and treatment of secondary osteoporosis in children zoledronic acid, alendronate, pamidronate (21). Simm et al. In 2018, two each-year dose of either 0. 1 mg/kg/year IV zoledronic acid or 9 mg/kg/year IV pamidronate were recommended for the treatment of primary and secondary osteoporosis in children. One year after treatment, the patient should be evaluated. If bone pain and bone fracture are present after this evaluation, BMD Z score is <-2, immobilization or steroid use continues, bisphosphonate treatment should be continued for another year (22).

In our study, bone pain and non-traumatic fracture frequency of patients decreased significantly after treatment. The mean total BMD and BMD Z-score values significantly increased by the DEXA measurement of the patients after bisphosphonate treatment. In studies investigating the effect of bisphosphonate treatment on bone pain and fracture frequency treatment on bone pain and fracture frequency, Celine et al. analyzed 24 studies. It was found that bisphosphonates were used to relieve bone pain caused by a wide variety of causes. Twenty of twenty-four studies have shown the effect of bisphosphonates in relieving pain in different pathologies (23). A notable decrease in bone pain was observed following treatment in research by Al-Agha et al. investigating the safety and effectiveness of zoledronic acid therapy in the treatment of secondary osteoporosis (24). In a study carried by Sees et al. in children with cerebral palsy, the frequency of fractures after pamidronate treatment in osteoporosis was evaluated. It has been reported that a significant decrease in the fracture rate was detected after treatment, and the most fractured bone before and after treatment was the femur (25).

In the study by Allington et al. in which cyclic pamidronate treatment was evaluated in secondary osteoporosis, including cerebral palsy and other neuromuscular diseases, a significant difference was found between the total BMD Z-scores of 18 patients examined before and 1 year after treatment (26). Naithani et al. found a significant increase in total BMD Z-score values before and after Zoledronic acid treatment in 27 patients with osteoporosis secondary to beta-thalassemia (27). Lee et al. showed a significant difference between pre-treatment and post-treatment total BMD Z-scores with pamidronate treatment of osteoporosis secondary to chemoterapy in acute lymphoblastic leukemia and nonHodgkin lymphoma patients (28). As supported by our data, it is seen that bisphosphonates are beneficial in the treatment of secondary osteoporosis and are an effective treatment in reducing bone pain and bone fractures.

It is well known that steroids have negative effects on bone metabolism and cause osteoporosis. In our study, when the total BMD parameters of patients using steroids and other patients before and six months after treatment were compared, it was determined that both groups were similarly affected at the time of osteoporosis diagnosis. In the literature, no studies were found in which the pre-treatment and post-treatment characteristics of secondary osteoporosis patient groups with and without chronic steroid medications use were examined. However, studies examining the treatment of patients with osteoporosis secondary to chronic steroid use were evaluated. In a group of pediatric patients with nephrotic syndrome who developed osteoporosis secondary to chronic steroid use, a significant increase was found in total BMD values at the 3rd month after pamidronate treatment (29). Ward. et al. investigated zoledronic acid treatment in 18 patients who developed osteoporosis secondary to steroids; a significant increase was found in the total BMD of the patients at the 12th month after zoledronic acid was administered (30).

In our study, only 1 (2.3%) patients receiving bisphosphonate treatment had side effects. The patient's current clinic, physical examination findings, and fever did not suggest an infectious condition. Also, there was no statistically significant difference between pre- and post-treatment Ca, P, ALP, vitamin D and PTH values. In the study by Ooi et al. no significant difference was found between serum Ca, P, ALP, and spot urine Ca/creatinine ratio before and 18 months after treatment, and serum bone metabolism biomarkers before and after treatment were found between normal limits as in our study (31). In a study by Munns et al., hypocalcemia developed in 74% of patients, fever in 52%, nausea/vomiting in 35%, and headache in 17% after zoledronic acid infusion in 63 patients with osteoporosis (32). Nosomyant et al. reported that flu-like symptoms developed in 7% of patients and hypocalcemia developed in 7% of patients after IV infusion of zoledronic acid and pamidronate in 123 patients diagnosed with osteoporosis (33). In another study by Högler et al. was reported that influenza-like symptoms were found in 85% of patients following iv zoledronic acid infusion (34). One of the possible reasons for the underreporting of side effects in our patients may be that the side effects of iv bisphosphonate treatment may have been less critical and not recorded because of their primary diseases.

There is no clear recommendation on how long bisphosphonates should be used in the treatment of osteoporosis in children. Side effects that may occur in long-term use of bisphosphonates are not yet known. In the pediatric age group, bone tissue is a growing tissue, and the hormonal status is different from that of adults. Considering these differences, the results of long-term use of bisphosphonates in children may be different from those in adults.

The strengths of our study are that it has a large series of secondary osteoporosis in childhood diagnosed in a single center, that the data of patients with and without steroid use can be evaluated, and that 6-month follow-up data are given.

In conclusion, secondary osteoporosis is a condition that is influenced by many factors, such as the primary disease causing osteoporosis, chronic medication use, especially steroids. If left untreated, osteoporosis leads to essential diseases such as bone pain, bone fractures, immobilization and reduced linear growth of bone. It is vital to early recognize ot these conditions that have a negative impact on bone health, and optimal care with vitamin D and calcium intake should be provided. Bisphosphonates are an effective treatment modality in treating childhood secondary osteoporosis and reducing the incidence of fractures resulting from osteoporosis.

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Table 1: Primary Disease Diagnoses of Patients with Secondary Osteoporosis

	n	**%**
Chronic inflammatory disease	34	55.7
Neuromuscular disease	16	26.2
Immunodeficiency	8	13.1
Acute Lymphoblastic Leukemia	5	8.2
Metabolic disease	5	8.2
Solid organ transplantation	5	8.2
Bone marrow transplantation	4	6.6
Epilepsy	4	6.6

Table 2. Findings of Patients Diagnosed with Secondary Osteoporosis at the Time of Admission

	Mean ± SD	Median (Min-Max)
Age (years)	11.89±4.88	11.6 (1.6-23)
Height SDS	-1.78±2.19	-1.64 (-9.60-1.80)
BMI **(Body mass index)**	17.91±4.56	17 (11-28)
BMI%	94.24±24.86	90 (61-180)
Pubertal status at admission	n	%
Prepubertal	33	54.1
Pubertal	28	45.9
	n	%
Chronic drug use	48	78.7
1. systemic steroid	36	25
2. chemotherapetics	14	23
3. immunomodulatory agent	12	19.7
4. antiepileptic		
5. inhaled steroids	5	8.2
6. L-Tyroxine	3	4.9
7. IVIG	2	3.3
8. antituberculosis drugs	1	1.6
9. testosterone	1	1.6
10. estrogen	1	1.6
11. growth hormone	1	1.6
	1	1.6
	n	%
Bone pain	29	49
	n	%
Vertebral fractures	61	100

Table 3. Clinical and Laboratory Values of Patients Diagnosed with Secondary Osteoporosis Before Bisphosphonate Treatment, and at the 6th Month of Treatment

	Before Treatment	6th Month After Treatment	Test Statistics	p value
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)		
Height SDS	-2.01±2.28 -1.72 (-9.60 – 1.80)	-1.93±2.11 -1.70 (-8 – 1.80)	Z=-0.369	0.712
BMI	17.47±4.51 16 (11-28)	17.52±4.59 17 (10-29)	Z=-0.557	0.577
% BMI	92.62±21.97 90 (61-150)	92.88±23.02 89 (58-150)	Z=-0.142	0.887
ALP (U/L)	204.35±166.84 176.5 (26-978)	209.03±178.40 183.5 (32-1004)	Z=-0.020	0.984
25OH Vitamin D (µg/L)	25.74±21.91 21.5 (3.6-118)	24.02±13.57 23.5 (1-67)	Z=-0.077	0.939
PTH (pg/ml)	57.34±68.80 36.5 (7-396)	53.14±40.97 41.2 (6-202)	Z=-1.117	0.264
Total BMD (gr/cm^2)	0.422±0.153 0.385 (0.165-0.830)	0.533±0165 0.510 (0.298-0.884)	t=-7.157	<0.001
Total BMC (gr)	16.90±10.18 14.88 (0.33-42.30)	21.33±10.50 19.00 (5.90-44.19)	Z=-4.766	<0.001
L_1-L_4 Area (cm^2)	35.36±9.77 33.00 (17.95-60)	36.96±9.51 37.27 (14.5-60)	t=-1.401	0.170
BMD Z Score	-3.88±1.28 -3.60 (-6.80 – -0.96)	-2.33±1.56 -2.30 (-6.20 – -0.67)	Z=-4.825	<0.001
BMD Z score by height	-3.19±1.75 -3.12 (-5.80 – 3)	-1.55±1.75 -1.76 (-6.20 – 3.30)	Z=-4.685	<0.001

Table 4. Comparison of the patients with chronic steroid use and others before bisphosphonate treatment, at the 6th month of treatment, and at their last follow-up.

	Patients Using Chronic Steroids			**Other Patients**		
	Before Treatment	**6th Month After Treatment**	**After Latest Treatment**	**Before Treatment**	**6th Month After Treatment**	**After Latest Treatment**
Age* (Year)	11.1±5.2	11.7±5.3	11.9±5.8	10.7±4.4	11.2±4.4	11.5±4.6
Height SDS*	-1.74±2.3	-1.72±1.9	-1.70±1.9	-2±2.3	-2±4.4	-1.3±2.6
BMI*	17.6±4.4	18.2±4.4	18±4.3	16.8±4.1	18.3±5.5	18.4±5.2
%BMI*	95±25	91.8±22.2	92.9±21.6	88.8±24	97.4±28.9	96.4±24.3
Bone Pain	%76	%28	%20	%40	%20	%20
Bone Fracture	%100	%40	%28	%100	%60	%50
Total BMC* (gr)	17.9±9.5	21.8±10.2	24.2±11.3	15.8±9.3	19.5±10	21.2±10
Total BMD* (gr/cm^2)	0.422±0.159	0.530±0.163	0.592±0.179	0.394±0.154	0.482±0.154	0.536±0.183
Total Area* (cm^2)	36.4±9.6	37.5±10.2	38.4±10.9	37±9.6	37.1±7.6	38.4±8.5

(*=Mean±SD for the analyzed parameters)

Table 5. Comparison of percent change in total BMD between steroid-treated patients and other patients

	Steroid	**Other**	Test Statistics	p value
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)		
Total BMD percentage change	19.77±9.95 20.14 (6.49-39.33)	37.09±35.76 27.27 (-9.80-111.51)	U=109.0	0.327

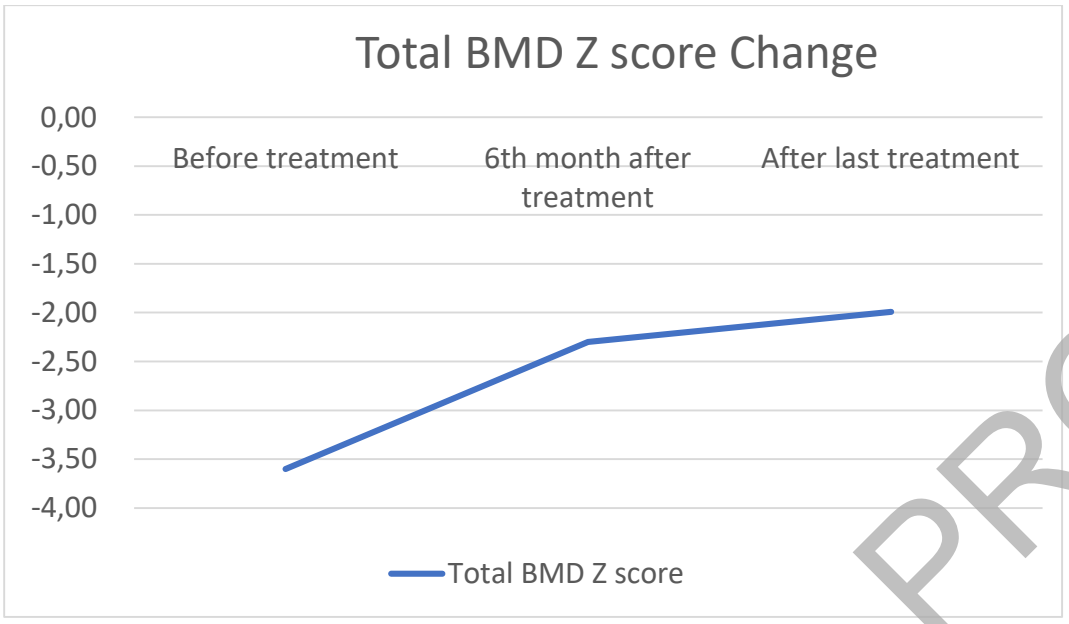

Figure 1. Median values of BMD Z-score of treated patients before treatment, 6 months after treatment and after the last treatment