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

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What is already known on 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 the long-term negative effects.

What this study adds?

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 the long-term negative effects. In this study, our objectives were to determine the diagnostic findings, treatment efficacy, and follow-up characteristics of children with secondary osteoporosis.

Methods: Patients diagnosed with secondary osteoporosis between January 2000 and January 2021 were included. The research was a cross-sectional and descriptive study. Study participants had to be under 18 years of age when the primary underlying disease was diagnosed and had received treatment for secondary osteoporosis. Patient data were collected from patient files. Statistical analysis was performed using Statistical Package for the Social Sciences, version 20.0 (IBM Corp, Armonk, NY, USA).

Results: Sixty-one patients (28 female; 45.9%) were evaluated. The most common underlying primary diseases were inflammatory diseases (57.7%), neuromuscular diseases (26.2%), immunodeficiency (13.1%), acute lymphoblastic leukemia (8.2%), metabolic diseases (8.2%), solid organ transplantation (8.2%), bone marrow transplantation (6.6%) and epilepsy (6.6%). The mean ± standard deviation chronological age when secondary osteoporosis was diagnosed was 11.89 ± 4.88 years. Patients were evaluated for osteoporosis at a mean of 6.39 ± 5.13 years after the onset of the underlying primary chronic diseases. Most (78.7%) had a history of one or more chronic drug use, including systemic steroids (59%), chemotherapeutics (23%), immunomodulatory drugs (19.7%), antiepileptic drugs (8.2%), inhaled steroids (4.9%), intravenous immunoglobulin (1.6%), and antituberculosis drugs 1.6%.Bone pain was detected in 49.2%. All patients had vertebral fractures before treatment. Bisphosphonate treatment was given to 45 (73.8%). There was a significant increase in mean bone mineral density (BMD) and bone mineral content six months after treatment (both $p < 0.001$). There was a significant increase in BMD Z-score values for chronological and height age (both $p < 0.001$). Overall mean BMD values increased by

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31.15% with treatment. Following bisphosphonate treatment, there was a significant reduction in both fracture number and bone pain ($p < 0.01$). Similar benefits from bisphosphonate treatment were evident in those who did or did not receive steroid treatment.
Conclusion: Secondary osteoporosis is a condition that is influenced by many factors, such as the primary disease causing osteoporosis and chronic medication use, especially steroids. If left untreated, osteoporosis may lead to clinically important morbidity (bone pain, fractures, immobilization) and reduced linear growth of bone. When used to treat childhood secondary osteoporosis, bisphosphonates significantly improve BMD and reduced fracture risk.
Keywords: Childhood, secondary osteoporosis, bisphosphonate

Introduction

Osteoporosis is closely associated with a higher risk of fracture due to a reduction in bone mass and degradation of the microarchitecture of the bone (1). A significant proportion of maximum bone mass is achieved during childhood and adolescence. Childhood is thus a significant period for bone health and 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 in children and adolescents without the presence of high-energy trauma, local disease, or a history of severe fractures with low bone density, it is considered osteoporosis (3). Osteoporosis can be divided into primary and secondary osteoporosis. Primary osteoporosis is caused by intrinsic skeletal problems, such as abnormalities in collagen, bone production, or bone mineralization. It can also be inherited. Otherwise, chronic drug usage or an underlying primary disease can result in secondary osteoporosis. Diseases leading to secondary osteoporosis in children can be grouped into neuromuscular diseases, endocrine disorders, metabolic diseases, chronic inflammatory diseases, and iatrogenic causes (4). Often, a clinical 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 more 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. In terms of the osteoporosis, treatment aims are to reduce bone pain, increase bone mass, reduce the risk of fractures, and increase patient mobility. Bisphosphonates, synthetic pyrophosphate analogs that bind to osteoclasts, inhibiting function and promoting 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, the aim was to determine the diagnostic findings in childhood secondary osteoporosis, to assess morbidities such as fractures and immobilization, to determine follow-up characteristics, and to investigate the efficacy of bisphosphonate treatments.

Methods

Patients diagnosed with secondary osteoporosis between January 2000 and January 2021 were included in the study. The study was retrospective, cross-sectional and descriptive. The protocol was approved by the Ethics Committee of Ankara University (approval number: İ7-441-20, date: 13.08.2020).

The underlying disease was defined as the "primary disease". Inclusion criteria were: aged <18 years at diagnosis of primary disease; currently being followed up in our clinic; the 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; two or more long bone fractures by age ten years; three or more long bone fractures by age 19 years; and had a history of conditions that carry a risk of osteoporosis including chronic use of drugs known to affect bone metabolism, diseases that cause immobilization, or other diseases that may affect bone metabolism, such as some hormonal deficiencies or anorexia nervosa.

Exclusion criteria were: BMD Z-score above -2 and long bone fractures; BMD Z-score above -2 and no vertebral fractures; no history of chronic systemic disease and/or drug use; and those with a genetic or clinical diagnosis of primary osteoporosis.

Patient data were extracted 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 recorded. Patients were followed up regularly every six months. During physical examination, anthropometric characteristics and pubertal

stages of the patients were evaluated. In anthropometric evaluation, body weight, height, height standard deviation (SD) score (SDS), body mass index (BMI), and BMI% were recorded and evaluated according to national reference data (7).

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

DEXA (Hologic Explorer N/S91724, Software version 13.3.0.1) was used to measure lumbar (L1-4) vertebral 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). DEXA measurements were performed before treatment, at the sixth month of treatment and during the follow-up period at 6 month intervals. The last measurements of BMD were also recorded.

Characteristics of bisphosphonate treatment dose and duration were analyzed. Patients were treated with bisphosphonate therapy and pamidronate, zoledronic asid, or alendronate were all used during the study period. Different bisphosphonate options were chosen according to the current approaches to osteoporosis treatment, drug availability, and the patient's treatment preference after diagnosis of secondary osteoporosis over the 20 year study period. 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 was given orally at a dose of 70 mg/week. Ca supplementation was given for 14 days following treatment. Oral elemental Ca 25-50 mg/kg/day was given. The dose was adjusted according to blood Ca level. Patients with vitamin D deficiency were given vitamin D3 at a treatment dose of 2000 IU/day for at least six weeks. Maintenance treatment was given at a dose of 400-1000 IU/day depending on the blood 25(OH)D3 levels (8).

Statistical Analysis

Statistical Package for the Social Sciences, version 20 was used for statistical analysis (IBM Corp, Armonk, NY, USA). Descriptive statistics include mean, SD, median, minimum and maximum for continuous data, and count and percentage values are given for discrete data. The 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 non-parametric data sets. 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-tabulation). A $p < 0.05$ was accepted as indicating statistical significance.

Results

The study included 61 patients (28 female; 45.9%). The most common underlying primary disease in patients with secondary osteoporosis was chronic inflammatory diseases (Table 1). The mean chronological age at the time of diagnosis of secondary osteoporosis was 11.89 ± 4.88 years and patients were evaluated for osteoporosis at a mean of 6.39 ± 5.13 years after the onset of underlying primary chronic diseases. At the time of diagnosis of secondary osteoporosis, the median height SDS (minimum-maximum height SDS) value was -1.64 (-9.60-1.80) and 23 (37.7%) had a height SDS below -2 SD and thus short stature. At the time of diagnosis, 54.1% were prepubertal (Table 2).

Chronic use of one or more drugs was present in 78.7%. These chronically taken drugs included systemic steroids (59%), chemotherapeutics (23%), immunomodulatory agents (19.7%), antiepileptic drugs (8.2%), inhaled steroids (4.9%), intravenous (iv) immunoglobulin (1.6%), and antituberculosis drugs (1.6%). Replacement therapies amongst patients included testosterone (1.6%), L-thyroxine (3.3%), estrogen (1.6%), and growth hormone (1.6%).

Bone pain was reported by 49.2%, and of these, 37.7% had low back pain. All patients had vertebral fractures before treatment (n = 61). Non-traumatic long bone fractures were present in 12.8% of the patients. The femur was

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

the most commonly fractured long bone (7.9%). Before endocrinological evaluation, the number of long bone fractures per year was 1 in 15.8% and 2 in 7.9% of cases.

The mean BMD of the cases included in the study was 0.47 ± 0.16 g/cm^2, and the BMD Z-score according to chronological age was -3.62 ± 1.16. Total BMC was 19.76 ± 10.51 g, and the mean BMD Z-score for height and age was -2.77 ± 1.63.

When the 25(OH)D3 levels of the cases were evaluated at the time of secondary osteoporosis diagnosis, the serum vitamin D level of 30 (49.1%) was below 20 ng/mL, and then vitamin D replacement was started. However, at the first six-month follow up after bisphosphonates, 17 (27.8%) had persistent serum vitamin D levels below 20 mg/mL despite vitamin D replacement.

Of the 61 patients, 45 (73%) received bisphosphonate treatment, and an additional two 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 biphosphonates, such as zoledronic asid, pamidronate, or alendronate. The minimum duration of bisphosphonate treatment was 6 months and maximum 4 years (mean 1.2 years, median 1 year). 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 mean of 1.00 ± 0.61 years. Ten patients (23.3%) received pamidronate treatment with a mean duration of 1.65 ± 1.08 years. One patient received alendronate and then pamidronate. Furthermore, two patients received pamidronate and then zoledronic acid.

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	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
Chronic drug use	n	%
1. Systemic steroid	48	78.7
2. Chemotherapetics	36	25
3. Immunomodulatory agent	14	23
4. Antiepileptic	12	19.7
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
Bone pain	29	49
Vertebral fractures	61	100

SD: standard deviation, BMI: body mass index, min-max: minimum-maximum, IVIG: intravenous immunoglobulin

With bisphosphonate treatment, there was an increase of 0.111 ± 0.09 g/cm^2 in the mean total BMD after six months of treatment ($p < 0.001$). Moreover BMD Z-scores increased six months after start of treatment ($p < 0.001$) (Figure 1). There was no difference between the mean area of L1-L4 vertebrae before and after treatment (Table 3). When the total BMD values of the patients before and after the last bisphosphonate treatment (mean treatment duration 1.10 ± 0.89 years) were compared, a mean increase of 0.169 ± 0.116 g/cm^2 was found ($p < 0.001$) with a mean increase of 31.15 ± 30.48% in the BMD values after six months of biphosphonate treatment compared to before treatment. However, there was no difference between the height SDS, BMI and BMI% of patients with secondary osteoporosis who received treatment before and six months after treatment. Pubertal progression was observed in eight patients. In only one case (2.3%), side effects were noted during bisphosphonate treatment. In this case, fever was recorded as an adverse effect approximately two hours after iv Zoledronic acid infusion.

There was a significant difference in reported bone pain and observed fracture rates before and after treatment with bisphosphanates ($p < 0.001$). Of the 27 patients with bone pain before treatment, the pain dissolved after treatment in 20 (74.1%). In 14 of 43 (32.5%) patients who had fractures before treatment, no fracture was detected after 6 months of treatment ($p < 0.05$). Only 1 of 32 (3.1%) patients without fracture had a non-traumatic fracture after treatment. Of note, no patients had long bone fractures after treatment.

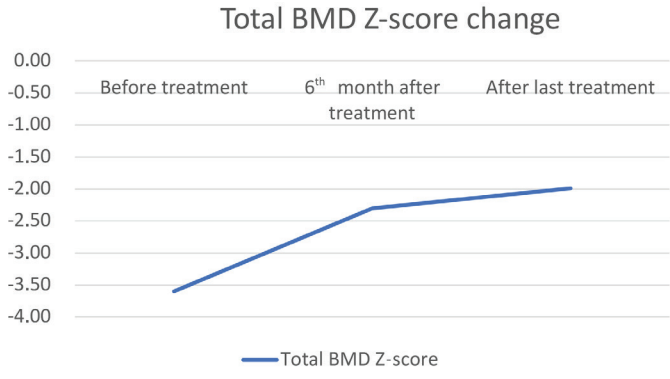

Figure 1. Median values of BMD Z-score of treated patients before treatment, six months after treatment and after the last treatment

BMD: bone mineral density

Thoracic and lumbar vertebral involvement significantly improved with treatment ($p < 0.01$). Of 26 patients with thoracic vertebrae pathology, improvement was seen in 11 (42.3%) patients with bisphosphonate treatment. Improvement in vertebral morphology (increase in vertebral BMD and height, reshaping of vertebral fractures) was seen in all cases with lumbar vertebral involvement ($n = 19$). There was no difference in the presence of scoliosis before and after treatment ($p > 0.05$). Serum Ca, P, alkaline phosphatase (ALP), vitamin D, and PTH levels did not differ between before and after biphosphonates ($p > 0.05$) (Table 3). Serum electrolytes were measured 4 hours, 24 hours and 1 week after the end of treatment. Hypocalcemia was not detected.

Cases with and without a history of steroids use were compared in terms of their response to bisphosphonate treatment (Table 4). There was an increase of 0.114 ± 0.086 g/cm^2 in the mean total BMD after the first six months of

Table 3. Clinical and laboratory values of patients diagnosed with secondary osteoporosis before bisphosphonate treatment, and at the sixth month of treatment

	Before treatment	Sixth 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
25(OH)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

SDS: standard deviation score, BMI: body mass index, min-max: minimum-maximum, IVIG: intravenous immunoglobulin, BMD: bone mineral density, BMC: bone mineral content, ALP: alkaline phosphatase, PTH: parathyroid hormone, 25(OH)D: 25-hydroxy vitamin D, SD: standard deviation

Table 4. Comparison of the patients with history of chronic steroid use and those without before bisphosphonate treatment, at the sixth month of treatment, and at their last follow-up

	Patients using chronic steroids			Other patients		
	Before treatment	Sixth month after treatment	After latest treatment	Before treatment	Sixth 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* (g)	17.9 ± 9.5	21.8 ± 10.2	24.2 ± 11.3	15.8 ± 9.3	19.5 ± 10	21.2 ± 10
Total BMD* (g/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.
SDS: standard deviation score, BMI: body mass index, BMD: bone mineral density, BMC: bone mineral content

bisphosphonate treatment in patients with chronic steroid use ($p < 0.001$). An additional 0.05 ± 0.118 g/cm^2 increase in BMD ($p < 0.05$) was seen between this time point and the median last examination (1 year). Similar increases in BMD were seen in those not given steroid treatment (0.087 ± 0.052 g/cm^2 in first six months and 0.053 ± 0.086 g/cm^2 up to the last examination; $p < 0.001$). There was no significant difference ($p > 0.05$) between the percentage change in total BMD values of patients on or not on steroids but chronically taking other drugs (Table 5).

Discussion

In this study, the diagnostic features and response to bisphosphonate therapy was evaluated in a large group of children and adolescents with secondary osteoporosis over a twenty year period. The most common type of 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. (11) 39 patients with secondary osteoporosis were analyzed and the mean age at diagnosis of secondary osteoporosis was 12 years. Zacharin et al. (12) reported that the mean age at diagnosis of secondary osteoporosis was 10.1 years in their series of patients with Duchenne muscular dystrophy.

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 are known to cause growth retardation. DEXA measurements in bone give areal measurement only and not volumetric values. DEXA measures a three-dimensional object in two dimensions spatially, and thus 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). Thus, we would like to stress that short stature should be assessed in cases with chronic disease and that evaluations should be adjusted accordingly.

Since the primary diseases examined in the present study and in earlier reports differ between centers, the age at diagnosis and the duration of development of osteoporosis after the primary disease may differ (14,15). Variables affecting this include the place/country where the centers are located, population differences and the clinical experience of the center (16,17). In our cohort, cases with secondary osteoporosis were referred to our pediatric endocrinology department fairly late after the diagnosis of the primary disease (6.39 ± 5.13 years). This suggests that there may be little awareness that bone health can be affected during various primary diseases, and secondary osteoporosis may be diagnosed late. Moreover, that the mean age of first fracture 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 minimizing morbidity. Focusing only on long bone fractures may delay diagnosis of secondary osteoporosis. In chronically ill patients who are at risk of secondary osteoporosis, risk factors should be investigated and lateral vertebral radiography may be justified, even in the absence of long bone fracture. We recommend that clinicians who follow chronically ill pediatric patients should evaluate them for osteoporosis with lateral vertebral radiography.

The most common type of 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 may 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 may 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 normal in the management of these diseases and 63.9% of our cohort had a history of systemic and/or inhaled steroid use. However, the characteristics of the cases with secondary osteoporosis

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

SD: standard deviation, min-max: minimum-maximum, BMD: bone mineral density

in the present study and in the literature may differ as well as exhibiting similarities. This is because factors, such as the heterogeneity of the patients' primary diseases, the demographics of study populations, the nature of the drugs used, and the different duration of drug use affect the results of the studies (18,19).

Vitamin D deficiency was detected in very nearly half of our cohort. Although replacement was given in cases with deficiency, vitamin D was still low in more than half (17/30) of these cases at the end of the six months follow-up. Optimal levels of vitamin D are crucial for maintaining bone health (20). Focusing on underlying problems may lead to neglect of checking vitamin D levels and thus failing to treat the deficiency, if any. Care should be taken to bring vitamin D levels to normal limits in chronically ill patients, to avoid having an avoidable negative effect on bone health. In patients with secondary osteoporosis, treatment of the etiology, if possible, will also prevent the negative effect on bone metabolism. If etiologic factors persist, it would be appropriate to evaluate bone health, eliminate vitamin D deficiency, and continue long-term follow-up of patients with osteoporosis, with appropriate management.

There is no consensus or treatment guideline for the treatment of secondary osteoporosis in children. In the present study, bisphosphonate treatment was administered to 45 patients over a period of 20 years in our clinic. Galindo-Zavala et al. (21) recommend zoledronic acid, alendronate and pamidronate for the treatment of secondary osteoporosis in children. Simm et al. (22) in 2018, treatment with 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/or bone fracture are present after this evaluation, the BMD Z-score is <-2, and immobilization or steroid use continues, bisphosphonate treatment should be continued for another year. In the present study, bone pain and non-traumatic fracture frequency of patients decreased significantly after treatment. The mean total BMD and BMD Z-score significantly increased by DEXA assessment after bisphosphonate treatment. Celin et al. (23) analyzed 24 studies investigating the effect of bisphosphonate treatment on bone pain and fracture frequency. These authors reported that bisphosphonates were used to relieve bone pain caused by a wide variety of causes. Twenty of twenty-four studies found a benefit of bisphosphonates in relieving bone pain due to different pathologies. A notable decrease in bone pain was observed following treatment in research by Al-Agha et al. (24) investigating the safety and effectiveness of zoledronic acid therapy in the treatment of secondary osteoporosis. In a study by Sees et al. (25) in children with cerebral palsy, the frequency of fractures after pamidronate treatment for osteoporosis was evaluated. It was reported that a significant decrease in the fracture rate was detected after treatment, although the most commonly fractured bone before and after treatment was the femur. In the study by Allington et al. (26) 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. Naithani et al. (27) 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. Lee et al. (28) 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 non-Hodgkin lymphoma. It has been shown that bisphosphonates are beneficial in the treatment of secondary osteoporosis and are an effective treatment in reducing bone pain and bone fractures, and this finding is supported by our study.

It is well known that steroids have negative effects on bone metabolism and cause osteoporosis. In the present study, when the total BMD parameters of patients using steroids and other patients before and six months after treatment were compared, it was found that both groups were similarly affected at the time of osteoporosis diagnosis. There are no published studies in which the pre-treatment and post-treatment characteristics of secondary osteoporosis patient groups with and without chronic steroid use were compared. However, studies examining the treatment of patients with osteoporosis secondary to chronic steroid use have been reported. 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 third month after pamidronate treatment (29). Ward et al. (30) investigated zoledronic acid treatment in 18 patients who developed osteoporosis secondary to steroids and a significant increase was found in the total BMD of the patients at the twelfth month after drug administration.

In the present study, only 1 (2.3%) patient receiving bisphosphonate treatment had side effects. The patient's clinical appearance, physical examination findings, and fever did not suggest an infectious condition. Furthermore, there was no significant difference between pre- and post-treatment Ca, P, ALP, vitamin D and PTH values. In the study by Ooi et al. (31) 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 to be within normal limits, as in our study. In a study by Munns et al. (32), 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. Nosomyant et al. (33) 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. In another study by Högler et al. (34) it was reported that influenza-like symptoms were found in 85% of patients following iv zoledronic acid infusion. One of the possible reasons for the low rate of side effects in our cohort may be that the side effects of iv bisphosphonate treatment may have been either less critical and or 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.

Study Limitations

The limitation of our study was the relatively short follow-up period in our patients treated for osteoporosis and the long term of follow-up of these patients is planned. Another limitation of our study is the use of different treatment protocols in the treatment of secondary osteoporosis during the long study period.The strengths of our study are that it was a large series of secondary osteoporosis in childhood diagnosed in a single center, that the data of patients with and without a history of chronic steroid use was compared, and that follow-up data at six months after treatment are given.

Conclusion

In conclusion, pediatric secondary osteoporosis is a condition that is influenced by many factors, such as the primary disease causing osteoporosis, and chronic medication use, especially steroids. This study also highlights that in children with chronic diseases, clinicians should evaluate the patient for osteoporosis based on risk factors. If left untreated, osteoporosis may lead to essential diseases, such as bone pain, bone fractures, immobilization and reduced linear growth of bone. It is important that early recognition of secondary osteoporosis is made and optimal care with vitamin D and Ca intake should be provided. It has been shown that bisphosphonates are an effective treatment modality in treating childhood secondary osteoporosis and reducing the incidence of fractures resulting from osteoporosis and these findings are supported by the results of the present study.

Ethics

Ethics Committee Approval: The protocol was approved by the Ethics Committee of Ankara University (approval number: İ7-441-20, date: 13.08.2020).

Informed Consent: The study was retrospective, cross-sectional and descriptive.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Emine Kübra Şen, Merih Berberoğlu, Gizem Şenyazar, Sirmen Kızılcan Çetin, Elif Özsu, Zehra Aycan, Zeynep Şıklar, Concept: Emine Kübra Şen, Merih Berberoğlu, Zeynep Şıklar, Design: Emine Kübra Şen, Merih Berberoğlu, Zeynep Şıklar, Data Collection or Processing: Emine Kübra Şen, Gizem Şenyazar, Sirmen Kızılcan Çetin, Ayşegül Ceran, Seda Erişen Karaca, Analysis or Interpretation: Emine Kübra Şen, Literature Search: Emine Kübra Şen, Zeynep Şıklar, Writing: Emine Kübra Şen, Merih Berberoğlu, Gizem Şenyazar, Sirmen Kızılcan Çetin, Elif Özsu, Zehra Aycan, Zeynep Şıklar.

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