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Research

Evaluation of Children with Secondary Osteoporosis: A Single-center Experience

Sekonder Osteoporoz Tanılı Çocukların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Children with chronic diseases are at a risk of inadequate bone mineralization due to the effects of the primary disease and/or treatment. The aim of this study was to evaluate the clinical characteristics and treatment responses of patients with secondary osteoporosis.

Methods: Forty-four patients with chronic diseases who had bone mineral density (BMD) Z-score of ≤-2.0 on the dual-energy X-ray absorptiometry (DXA) were included.

Results: Age at diagnosis of osteoporosis was 9.2±4.9 years (1.4-17.7 years). Chronic disease groups were defined as gastrointestinal (29.5%), neurological (22.7%), hematologic (18.2%), inborn errors in metabolism (11.4%), rheumatologic (9.1%), and renal (9.1%). The rate of receiving steroid treatment was 63.6%. DXA Z-score was -2.8±0.9. The fracture frequency in the long bones was 20.5%. Bisphosphonate (BP) treatment was given in 34.1% (n=15) of the patients. BP was the most commonly used in neurological diseases (50%). A significant difference was found between the initial and final DXA Z-scores in BP patients (-3.3±1.0 and -2.4±0.9; p=0.004).

Conclusion: In our study, a heterogeneous group of chronic systemic diseases was evaluated, and BP treatment provided a significant improvement in BMD. Further prospective studies are still required in which clinical and radiological improvements are evaluated in large groups of patients.

Keywords: Bisphosphonates, secondary osteoporosis, pediatric endocrinology

ÖZ

Amaç: Kronik bir hastalık nedeniyle izlenen çocuklar, hastalığın etkileri ve/veya tedaviye bağlı olarak yetersiz kemik mineralizasyonu riski taşımaktadırlar. Kronik hastalıklara bağlı osteoporozu olan hastaların klinik özelliklerinin ve tedavi yanıtlarının değerlendirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Kronik hastalık nedeniyle izlenen, dual-enerji X-ışını absorbsiyometri (DXA) ile vertebra kemik mineral yoğunluğu (KMY) boy yaşına göre Z-skorunun ≤-2.0 olan 44 hasta çalışmaya alındı.

Bulgular: Osteoporoz tanı yaşı 9,2±4,9 yıl (1,4-17,7) idi. Kronik hastalık grupları gastrointestinal (%29,5), nörolojik (%22,7), hematolojik (%18,2), doğumsal metabolik (%11,4), romatolojik (%9,1) ve renal (%9,1) olarak belirlendi. Steroid tedavisi alma oranı %63,6 idi. DXA Z-skoru -2,8±0,9 idi. Uzun kemiklerde kırık oranı %20,5 idi. Hastaların %34,1'inde (n=15) bifosfonat (BP) tedavisi verilmişti. BP, en sık nörolojik hastalıklarda (%50) kullanılmıştı. BP alanlarda başlangıç ve son DXA Z-skorları arasında anlamlı fark saptandı (-3,3±1,0 ve -2,4±0,9; p=0,004).

Sonuç: Çalışmamızda farklı hastalık gruplarından heterojen bir grup değerlendirilmiş olup BP tedavisinin KMY'de anlamlı bir düzelme sağladığı görülmüştür. Her hastalık grubu için büyük gruplarda klinik ve radyolojik düzelmenin birlikte değerlendirildiği prospektif çalışmalara gereksinim vardır.

Anahtar Kelimeler: Bifosfonat, sekonder osteoporoz, pediatrik endokrinoloji

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INTRODUCTION

Osteoporosis is characterized by microarchitectural deterioration of bone tissue and low bone mass. According to the pediatric position statements of the International Society of Clinical Densitometry (ISCD), osteoporosis in children is defined by the presence of a clinically significant fracture or a significant fracture history and a low bone mineral density (BMD) (1-3). The use of ISCD criteria to define osteoporosis in children has been challenged, nowadays. Hence, taking into account underlying conditions and fracture risk, signs of a monogenic disorder, glucocorticoid (GC) use, and clinical features of fracture are accepted as a more contemporary view (4).

Osteoporosis is classified as primary and secondary osteoporosis (SO). There are many significant causes of bone fragility causing primary osteoporosis (PO) such as osteogenesis imperfecta (OI). Nonetheless, osteoporosis in children is usually secondary to chronic systemic illness or its treatment. Using GCs reduces bone strength and results in increased fragility, and consequently fractures (1).

Bisphosphonates (BP) are widely used for treating osteoporosis, due to their effect on preventing the loss of bone density (1). Some report that short-term use of BPs appears well-tolerated. The evidence for BPs in SO treatment remains inadequate. For this reason, more studies have been planned that focus on the efficacy and safety of BPs in SO treatment in children.

In this study, our aim was to describe the characteristics of our patients with SO who had different etiologies for their bone fragility and to define the treatment responses to BPs.

METHODS

A retrospective observational study was performed in 132 patients with pediatric osteoporosis in the Pediatric Endocrinology Unit of the İstanbul University, İstanbul Faculty of Medicine.

The anthropometric, clinical, laboratory, and radiologic data were obtained from the patient records. The osteoporosis cohort included 88 patients with PO (n=83 OI, n=4 osteoporosis pseudoglioma syndrome, n=1 spondyloocular syndrome), and 44 patients with SO. Patients with SO were referred from the various departments of pediatrics who were in the follow-up due to different types of chronic diseases.

The study was approved by the Local Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021).

Pubertal development was assessed according to Tanner's stages. Weight and height were measured in all subjects, using a wall-mounted calibrated Harpenden Stadiometer (Holtain Ltd.) and electronic scale (sensitivity to 0.1 kg). Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). All measurements were expressed as standard deviation scores (SDS) according to national standards (5).

ISCD criteria were used to define osteoporosis:

i. One or more vertebral compression fractures in the absence of high-energy trauma or local disease, regardless of the BMD Z-score.

ii. The presence of BMD Z-score ≤-2.0 and a clinically significant fracture [in the absence of vertebral fractures (VF)].

Clinically significant fractures were defined as follows:

a) Two or more long bone fractures by the age of 10 years;

b) Three or more long bone fractures at any age up to 19 years (3).

Intravenous (IV) BP (pamidronate) was applied (3 mg/kg/dose) and repeated every 3-6 months (6). Oral alendronate was administered at a dose of 70 mg/week.

Oral vitamin D (1200 U/day) and calcium (Ca) supplementation (500-1000 mg/day) were used at recommended doses (7). The doses were adjusted according to Ca and 25-hydroxyvitamin D [25(OH)D] serum levels. 25(OH)D below 20 ng/mL was accepted as 'deficiency', and between 21-29 ng/mL was considered 'insufficiency'.

Those with fractures and/or compression fractures of the vertebrae were primarily treated with BPs in addition to vitamin D and Ca.

Biochemical Assays

The quantitative determination of Ca in the serum was studied with the photometric method (Roche/Hitachi Cobas C system). The range of measurement of this test is 0.8-20.1 mg/dL. The quantitative determination of phosphorus (P) in the serum was also done by the photometric method (Roche/Hitachi Cobas C system). The measurement range of the test is 0.31-20 mg/dL. Alkaline phosphatase was measured using the photometric method (Roche/Hitachi Cobas C system). The measuring range of the test was 5-1200 U/L. Parathyroid hormone was measured by the electrochemiluminescence method (Modular Analytical E170 device). The range of measurement of the test was 1.2-5000 pg/mL. 25(OH)D was measured using the high-performance liquid chromatography.

Imaging

BMD was evaluated using DXA with a Hologic QDR 4500A Fan Beam X-ray Bone Densitometer (Hologic, Bedford, MA) and analyzed using software version 12.3. BMD results are presented in Z-scores, which are in SDS relative to mean values for equipment-specific age and sex-matched national data (8). Volumetric BMD was calculated from the spine (L1-L4). The formula of Carter et al. (9), which is bone mineral content/area1.5 was used.

Statistical Analysis

The data were analyzed using the SPSS for Windows software package, version 21.0 (SPSS, Chicago, IL). Data were tested for normality distribution using the Shapiro-Wilk test. Descriptive statistics were used to summarize all variables of interest. Categorical data were reported as frequencies and percentages. Continuous variables are expressed as mean ± SDs. A nonparametric t-test was used for the comparison of numeric and χ^2 tests for categorical variables. Pearson or Spearman analyses were used to determine the correlations between the clinical parameters. A p-value of <0.05 was considered as statistically significant.

RESULTS

In this study, SO constituted 33.3% (n=44) of our pediatric osteoporosis cohort. The clinical data of the patients with PO were reported previously by our group (10-12). Patients with SO (22 females) who were followed up with various chronic diseases and referred to endocrinology for the monitorization of endocrine side effects related to primary condition and/or treatments, were enrolled.

Those with BMD Z-scores ≤-2.0 on the DXA (lumbar spine) and/or patients with history of significant fractures, constituted the study group (according to the criteria described above).

The mean age of diagnosis of the primary disease (chronic disease) was 3.4±3.9 years (median 2.4, range: 0.0-15.3 years) in our SO cohort. The mean age of diagnosis of SO was 9.2±4.9 years (range:1.4-17.7 years). Primary chronic diseases were classified as gastrointestinal (29.5%), neurologic (22.7%), hematologic (18.2%), inborn errors in metabolism (11.4%), rheumatologic (9.1%), and renal (9.1%) (Figure 1). The distribution of chronic diseases according to the primary etiology is demonstrated in Table 1. The ratio of those receiving GC treatment was 63.6%. The mean values of height and BMI SDS at admission to endocrinology were -1.4±1.4 and -0.3±1.8, respectively. The ratio of short stature (height <-2.0 SDS) was 30.2%. Twenty-seven patients (61.4%) were prepubertal, at admission. Only two patients (2 female) had pubertal delay (4.5%), and their primary diseases were thalassemia major (with bone marrow transplantation) and epilepsy (due to tuberous sclerosis). Two patients had VF (4.5%) and eight patients (18.1%) had complaints of back pain, in the cohort.

The mean value of the DXA Z-score was -2.8±0.9 and 20.5% of the patients had a history of long bone fractures. There was no correlation between the type of chronic disorder and the presence of long bone fractures (r=0.03, p=0.847) and no correlation with the number of long bone fractures (r=0.075, p=0.848). Vitamin D deficiency was detected in 10 patients at admission (22.7%), and it was most frequently encountered in patients with gastrointestinal disorders.

The mean time period for the follow-up of these patients in the endocrinology unit was 4.6±3.3 years.

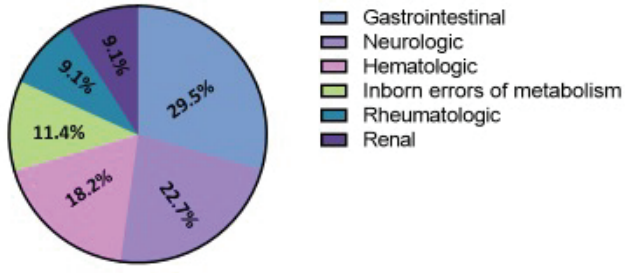

Figure 1. The ratio of chronic diseases in the secondary osteoporosis cohort

Table 1. The distribution of primary chronic diseases causing secondary osteoporosis

Disease group	n (%)	The type of primary disease
Gastrointestinal diseases	13 (29.5)	Chronic liver disease (n=8), Crohn disease (n=3), celiac disease (n=1), chronic pancreatitis (n=1)
Neurologic diseases	10 (22.7)	Duchenne muscular dystrophy (n=5), tuberous sclerosis and epilepsy (n=1), epilepsy (n=1), lomber meningomyelocele and hydrocephaly (n=2), cerebral palsy (n=1)
Hematologic diseases	8 (18.2)	Malignancy (n=4), bone marrow transplant (n=2), thalassemia major (n=1), chronic immune thrombocytopenic purpura (n=1)
Inborn errors of metabolism	5 (11.4)	Galactosemia (n=2), glycogen storage disease (n=1), fructose 1,6 bisphosphotase deficiency (n=1), lysinuric protein intolerance (n=1)
Rheumatologic diseases	4 (9.1)	Juvenile idiopathic arthritis (n=4)
Renal diseases	4 (9.1)	Nephrotic syndrome (n=2), renal tubular acidosis (n=1), chronic renal failure secondary to hemolytic uremic syndrome (n=1)

Fifteen patients (34.1%) received BP therapy (pamidronate n=14, zoledronate n=1, and alendronate n=1). One patient was transferred to zoledronate due to allergic reactions to pamidronate treatment. No other complications besides flu-like symptoms and mild hypocalcemia were observed during the follow-up. Pamidronate was used in a dose of 1-3 mg/kg (IV) in a 3-6-month period. The mean cumulative dose was 12.8±8.7 mg/kg (range: 3.0-33.0 mg/kg). Fifty percent of the patients treated with BP were in the neurological disorder group.

BMD Z-scores of the patients who received BPs at admission and last evaluation were -3.3±1.0 and -2.4±0.9, respectively (p=0.004). BMD Z-scores of the patients who do not receive BP therapy at admission and at the last evaluation were, -2.5±0.8 and -2.5±1.1, respectively (p=0.075).

The clinical characteristics and response to BP therapy in patients with SO are demonstrated in Table 2.

DISCUSSION

The life expectancy of patients with chronic systemic diseases has been significantly increased; therefore, long-term morbidities such as osteoporosis have become an important issue (2). In this study, we described the characteristics of patients with SO with various chronic diseases and the responses to BP therapy.

Most of the chronic diseases or their treatment affect BMD and cause fractures. Hence, osteoporosis in children is usually secondary to chronic illness or its treatment (1). In our pediatric osteoporosis cohort, SO constituted only one-third of the cases. This may be explained by well care of the primary disease, prevention of immobilization, abstaining from high-dose and long-term GCs or more frequent referral of PO to a tertiary center.

Table 2. **The clinical characteristics and response to bisphosphonate therapy in patients with secondary osteoporosis**

Clinical characteristics of the patients		
	At admission	**At the last evaluation**
Age (years)	9.2±4.9	13.5±4.5
Height SDS	-1.4±1.4	-1.5±1.4
BMI SDS	-0.3±1.8	0.2±2.5
Response to BP therapy		
	DXA Z-score at admission	**DXA Z-score at the last evaluation**
BP therapy (+) (n=15)	-3.3±1.0*	-2.4±0.9*
BP therapy (-) (n=29)	-2.5±0.8	-2.5±1.1

*Defines p<0.05
BP: Bisphosphonate, SDS: Standard deviation scores, BMI: Body mass index, DXA: dual-energy X-ray absorptiometry

The most frequent conditions that cause SO are inflammatory diseases (causing malabsorption), myopathies such as Duchenne muscular dystrophy, malignancies, thalassemia, immobilization, and hypogonadism (1,2,13). In our cohort, approximately one -third of the patients had gastrointestinal disorders causing SO. This is particularly related to the additive effects of malabsorption of lipid-soluble vitamins causing 25(OH)D deficiency, despite the suggestion of routine vitamin supplements by gastroenterologists. In accordance with this, 25(OH)D deficiency was also most frequent in the gastrointestinal disorder group, in our cohort.

Systemic GCs increase bone resorption, inhibit bone formation, and consequently decrease peak bone mass (14). Using oral GCs for more than 3 months and greater than 5-7.5 mg/day of prednisone (or equivalent), increases the fracture risk (15). GC excess adversely affects muscle mass/function, causing myopathy and increased risk of falls, which is another risk factor for fractures (16). In our cohort with chronic diseases, more than half of the patients had received or were still receiving GC therapy.

Some medications adversely affect bone quality due to altered Ca and 25(OH)D metabolism, due to the induction of the cytochrome P450 enzyme by the anticonvulsants such as phenytoin, phenobarbital, and carbamazepine, increase the risk of fragility fractures. Therefore, Ca and vitamin D must be supplemented in patients who use these medications (16,17). In our unit, oral vitamin D and Ca supplementation were offered at recommended doses, and in cases, with deficient vitamin D higher doses were applied. Nonetheless, the type of drugs used for primary disease, compliance problems due to multiple drug use, immobilization and inadequate exposure to the sun, and malabsorption of lipid-soluble vitamins may all affect the Ca and vitamin D status of these patients.

Patients who have recurrent fractures or having orthopedic surgery that requires better bone quality, with low BMD will require treatment (16,18). In immobilized children, the estimated prevalence of fragility fractures was 20%. Indeed, immobilization is mostly a problem for children with neurologic disorders, and they constituted the second most frequent cause of SO in our cohort. SO is a severe complication in neurologic diseases such as, muscular dystrophies, and cerebral palsy (19). The ratio of using BPs was highest in the patients with neurologic diseases in our

study, most likely due to the above-mentioned problems of mobilization.

The main manifestation of both PO and SO is VFs, hence routine screening is necessary. VFs can often be asymptomatic and recognized on routine screening (16). Lateral spine radiographs can be of limited quality when diagnosing VFs, and radiation exposure is the main drawback to its use. Symptoms of back pain may be an alerting sign for the VFs. Two patients had VF (4.5%) and eight patients (18.1%) had complaints of back pain, in our cohort. However, some mild cases of vertebral compression may be missed upon the infrequent application of X-rays due to the fear of radiation exposure.

BPs inactivate/inhibit osteoclast formation and act as an anti-resorptive agent. They improve the acquisition of bone mass, reducing the fracture rate in some forms of osteoporosis (19). Although, it has been now replaced in most centers by the more potent zoledronate, pamidronate has been used most extensively up to date. Oral BPs, mainly alendronate and risedronate, are less frequently used in children. IV and oral BPs increase BMD in children, as confirmed in other previous studies reporting the use of BPs in SO (2,16,20). In our cohort, about one-third of the patients were treated with BPs. We have observed that the BMD Z-score of those receiving BPs was significantly higher compared with those who do not receive treatment.

Several conditions have been associated with SO, mostly the use of GCs, systemic inflammation, hypogonadism, and immobility. Children with these conditions should be screened with DXA and lateral spine images at diagnosis and should be followed with repeated assessments (16).

CONCLUSION

In our study, a heterogeneous group of chronic systemic diseases was evaluated and we have seen that BP therapy provided a significant improvement in BMD Z-scores and clinical findings. Furthermore, prospective studies must guide clinical practice in children with SO, as all medications used for pediatric osteoporosis are still based mainly on clinical experience.

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ETHICS

Ethics Committee Approval: The study was approved by the Local Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Z.Y.A., F.B., Ş.P., A.P.Ö., R.B., F.D., Concept: Z.Y.A., F.B., F.D., Design: Z.Y.A., F.B., Ş.P., A.P.Ö., R.B., F.D., Data Collection or Processing: Z.Y.A., F.B., A.P.Ö., R.B., Analysis or Interpretation: Z.Y.A., F.B., Ş.P., F.D., Literature Search: Z.Y.A., Writing: Z.Y.A., F.B., Ş.P., F.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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