ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of the Children with Secondary Osteoporosis: A Single-Center Experience

Sekonder Osteoporoz Tanısı Alan Çocuk Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Introduction: Osteoporosis is a skeletal disease characterized by low bone mass, which increases the risk of fractures and can arise from primary or secondary causes. The aim of this study is to evaluate the frequency and causes of secondary osteoporosis diagnosis in patients presenting to our clinic, as well as to assess the clinical characteristics and treatment responses of these patients.

Materials and Methods: Seventy patients with secondary osteoporosis, who were followed and treated for at least two years due to chronic disease, were included in the study. The clinical characteristics, comorbidities, medications used, laboratory tests, Dual X-ray Absorptiometry (DXA) scans, magnetic resonance imaging results, and treatment protocols of the patients were evaluated.

Results: The mean age of the patients was 10.37±3.81 years. The mean age at diagnosis of the primary disease (chronic illness) was 4.47±3.54 years. The mean duration for the development of osteoporosis was 5.76±4.31 years. Among the cases, 21 (30%) had oncological, 15 (21.5%) had rheumatological, 11 (15.7%) had nephrological, 11 (15.7%) had hematological, 4 (5.7%) had neurological diseases, and 8 (11.4%) had other diseases. Of the patients, 35 (50%) had a history of steroid use, 16 (22.9%) used both steroids and methotrexate (MTX), 10 (14.3%) used MTX, and 9 (12.9%) used antiepileptic drugs. The mean vertebral DXA Z-score before treatment was -3.06±1.05, while the DXA Z-scores at the 1st and 2nd years of treatment were -2.51±1.09 and -2.16±1.15, respectively. A significant difference was found between the pre-treatment and 1st and 2nd year DXA Z-scores ($p<0.001$).

Conclusion: In our study, patients with secondary osteoporosis caused by various chronic diseases and their treatments were evaluated. With treatment, significant positive changes in bone mineral density and clinical findings were observed. There is a need for the development of guidelines for the diagnosis, treatment, and follow-up of secondary osteoporosis patients and for the creation of larger databases through prospective studies to guide clinical practices.

Keywords
Secondary osteoporosis, bone mineral density, Dual X-ray Absorptiometry

Anahtar kelimeler
Sekonder osteoporoz, kemik mineral yoğunluğu, Dual X-ray Absorbsiyometri

Öz

Giriş: Osteoporoz, kırık riskinde artış yapan, primer ya da sekonder nedenlerle ortaya çıkabilen, düşük kemik kitlesi ile karakterize bir iskelet hastalığıdır. Bu çalışmanın amacı, kliniğimize başvuran hastaların ne sıklıkta ve hangi nedenlerle sekonder osteoporoz tanısı aldığını, hastaların klinik özelliklerinin ve tedavi yanıtlarının değerlendirilmesidir.

Gereç ve Yöntem: Kronik hastalık nedeniyle izlenen, sekonder osteoporoz tanısı alıp en az iki yıl takip ve tedavi edilen 70 hasta çalışmaya dahil edildi. Hastaların

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klinik özellikleri, ek hastalıkları, kullandığı ilaçlar, laboratuvar testleri, Dual X-ray Absorbsiyometri (DXA) taraması ve manyetik rezonans görüntüleme sonuçları ve tedavi protokolleri değerlendirildi.
Bulgular: Hastaların ortalama yaşı 10,37±3,81 yıldı. Primer hastalığın (kronik hastalık) ortalama tanı yaşı 4,47±3,54 yıldı. Osteoporoz gelişme süresi ortalama 5,76±4,31 yıldı. Olguların 21'inde (%30) onkolojik, 15'inde (%21,5) romatolojik, 11'inde (%15,7) nefrolojik, 11'inde (%15,7) hematolojik, 4'ünde (%5,7) nörolojik hastalık ve 8'inde (%11,4) diğer hastalıklar tespit edildi. Hastaların 35'inde (%50) steroid, 16'sında (%22,9) steroid ve metotreksat (MTX), 10'unda (%14,3) MTX, 9'unda (%12,9) antiepileptik ilaç kullanım öyküsü vardı. Tedavi öncesi, ortalama vertebral DXA Z skoru -3,06±1,05 iken 1. yıl ve 2. yılda DXA z skorları sırasıyla -2,51±1,09 ve -2,16±1,15 idi. Tedavi öncesi ile 1. yıl ve 2. yıl DXA z skorları arasında anlamlı fark saptandı ($p<0,01$).
Sonuç: Çalışmamızda, çeşitli kronik hastalıkların ve tedavilerinin neden olduğu sekonder osteoporoz hastaları değerlendirildi. Tedavi ile, kemik mineral yoğunluğu ve klinik bulgularda anlamlı pozitif değişiklik saptadık. Sekonder osteoporoz hastalarının tanı, tedavi ve takip kılavuzlarının geliştirilmesi ve klinik pratikleri yönlendirmek için prospektif çalışmalarla daha geniş veri tabanlarının oluşturulmasına ihtiyaç bulunmaktadır.

Introduction

Osteoporosis is a global health issue characterized by decreased bone mineral density (BMD) and disruption of bone microarchitecture, which increases bone fragility and susceptibility to fractures. Pediatric osteoporosis can present primarily as osteogenesis imperfecta (OI) and idiopathic juvenile osteoporosis (IJO), or secondarily due to long-term treatments for various chronic diseases or as a result of immobilization (1,2). The complication of treating chronic diseases in childhood, resulting in prolonged life spans, provides sufficient time for the development of osteoporosis. Consequently, pediatric osteoporosis has become increasingly common in recent years. Fractures resulting from osteoporosis can lead to pain and reduced quality of life in pediatric patients (3). Therefore, it is crucial to diagnose the condition quickly and accurately to begin treatment as soon as possible.

The diagnosis of osteoporosis is made based on the concordance of clinical findings and Dual X-ray Absorptiometry (DXA) results. According to the 2019 report by the International Society of Clinical Densitometry (ISCD), pediatric osteoporosis is defined by the presence of a clinically significant fracture or a significant fracture history along with low BMD (4). Therefore, to diagnose a child with osteoporosis, there must be both reduced bone mass and the presence of fractures.

Deciding whether and when to start treatment in children is challenging. The clinical disease spectrum is broad, and therefore a one-size-fits-all treatment strategy does not exist. Important factors to consider include, among others, the presence of symptoms (e.g., back pain or musculoskeletal pain), the nature and severity of any underlying condition, the level of mobility, and the likelihood of spontaneous or medication-assisted recovery. For instance, the timing and recovery potential of osteoporosis related to leukemia are completely different compared to osteoporosis due to Duchenne muscular dystrophy, thus requiring different treatment approaches and durations (5).

In our study, we aimed to examine the clinical features of patients diagnosed with secondary osteoporosis, the underlying causes, pre- and post-treatment DXA results, laboratory tests, and the treatment protocols they received. By determining the relationship of this condition with fractures, we also aimed to review these causes alongside a literature review.

Materials and Methods

Study Design and Data Collection

Data of patients diagnosed with osteoporosis at the Pediatric Endocrinology Clinic of Akdeniz University between January 2019 and January 2023 were retrospectively reviewed from hospital and file records.

Patients who were followed up for at least two years after diagnosis and received treatment were included in the study. The patient data of a total of 176 patients were reviewed. Thirty-two patients were excluded from the study due to having a diagnosis of OI and three due to having a diagnosis of IJO (Idiopathic Juvenile Osteoporosis). Forty-one patients with a follow-up period of less than two years were excluded from the study. Thirty patients with missing DXA information in their files were also excluded from the study. A total of 70 patients were included in the study (Figure 1).

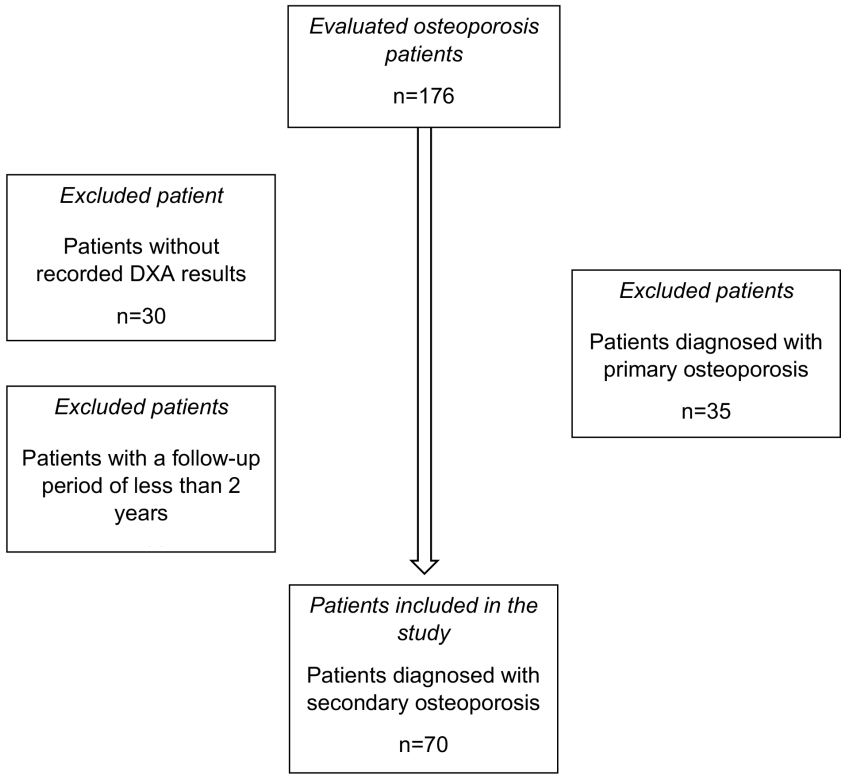

Figure 1. Working flow chart

The clinical features, underlying etiologies, laboratory tests, DXA scan results, treatment protocols, and the duration and types of previous medication treatments of the patients were evaluated. Data were recorded at the start of treatment and at the 1st and 2nd years of treatment. After the baseline DXA scan, the DXA results at the 1st and 2nd years of treatment were recorded to assess the effectiveness of the treatment. MRI data were recorded to evaluate vertebral compression fractures before treatment and at the 1st and 2nd years of treatment. Our cases were evaluated in accordance with the Helsinki Declaration. Approval for the study was obtained from the Ethics Committee of Akdeniz University (date: 25.01.2023, approval number: 70904504/64).

Identification and Diagnostic Procedure

ISCD criteria were used to define osteoporosis (6):

I. One or more vertebral compression fractures in the absence of high-energy trauma or local disease, independent of BMD z-score

II. BMD Z-score ≤-2 with a history of clinically significant fracture in patients without vertebral compression fractures

Clinically significant fractures were defined as:

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

The anthropometric, clinical, laboratory, and radiological data of the patients were obtained from patient records. Height and body weight measurements were taken using a wall-mounted, calibrated Harpenden Stadiometer (Holtain Ltd.) and an electronic scale with 0.1 kg precision. The patients' height, height standard deviation score (SDS), body weight, body weight SDS, body mass index (BMI), and BMI SDS values were recorded. BMI was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m²). Each anthropometric measurement's SDS was calculated according to Turkish children's standards (7).

Imaging

BMD measurement, the lumbar region (L1-L4) was assessed using DXA (QDR 4500, Hologic Inc., Bedford, MA, USA). The BMD results were expressed as Z-scores in SDS, based on age- and gender-matched

national reference data specific to the equipment used (8). Magnetic resonance imaging (MRI) was utilized to evaluate vertebral compression fractures.

Biochemical Analyses

Serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxy vitamin D [25(OH)D], urine Ca, and urine creatinine levels were analyzed. Serum and urine Ca, P, and ALP were measured using a colorimetric method on the Roche Cobas 8000 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). PTH was measured using the "Electrochemiluminescence Immunoassay" (ECLIA) method on the Roche Modular Analytics E170 Immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Urine creatinine was measured using the Modified Jaffe method on the Roche Cobas 8000 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). 25(OH)D was measured using a chemiluminescence immunoassay method on the Siemens Centaur XP device (Siemens Healthcare Diagnostics, Forchheim, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0. Categorical measurements were presented as numbers and percentages, while continuous measurements were presented as mean ± SD or median (interquartile range). The Shapiro-Wilk test and the Kolmogorov-Smirnov test were used to determine whether the parameters in the study followed a normal distribution. For the comparison of continuous measurements between groups, distributions were checked, and for parameters that did not show a normal distribution, a p-value of less than 0.05 obtained from the Wilcoxon test was considered significant. For repeated measures, a p-value of less than 0.016 obtained from the Friedman test was considered significant.

Results

Of the 70 cases included in the study, 36 (51.4%) were male and 34 (48.6%) were female. The mean age of the patients was 10.3±3.8 years. The mean height SDS was -3.0±2.5, the mean body weight SDS was -1.9±2.9, and the mean BMI SDS was -0.1±1.9.

In our study, the average age at diagnosis of the primary disease (chronic disease) was 4.47±3.54 years. The average time to develop osteoporosis after being diagnosed with a chronic disease was 5.76±4.31 years. Among the cases, 21 (30%) had oncological diseases, 15 (21.5%) had rheumatological diseases, 11 (15.7%) had nephrological diseases, 11 (15.7%) had hematological diseases, 4 (5.7%) had neurological diseases, and 8 (11.4%) had other diseases (Figure 2).

Among the patients, 35 (50%) had a history of steroid use, 16 (22.9%) had used both steroids and methotrexate (MTX), 10 (14.3%) had used MTX, and 9 (12.9%) had a history of using antiepileptic drugs (Figure 3). The median duration of drug use was 0.96 (2.92) years. The average dose of steroid therapy, calculated as the equivalent of hydrocortisone in mg/m²/day, was 41.81±22.72 at the time of presentation.

At the time of presentation, seven (10%) cases had fractures, while 63 (90%) cases did not. During follow-up, a fracture was observed in one (1.4%) patient, whereas 69 (98.6%) did not have any fractures. In the MRI evaluations before treatment, two patients had vertebral compression fractures, but no fractures were

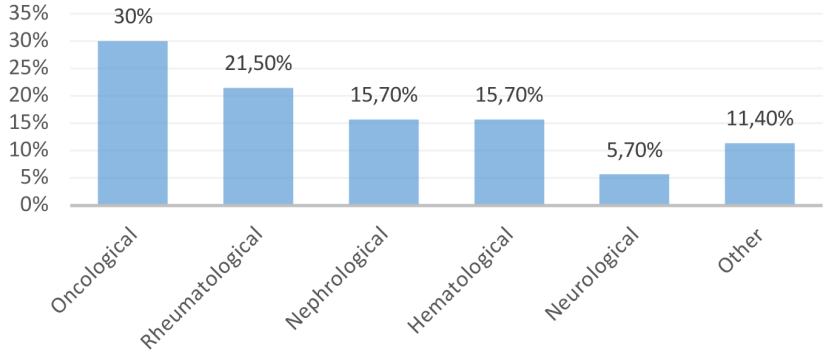

Figure 2. Classification of patients by etiology

detected in the MRIs assessed in the first and second years of treatment.

At the time of presentation, 24 (34.3%) patients had various complaints such as low back pain, widespread bone pain, and pain in the lower extremities, while 46 (65.7%) had no complaints. In treatment, 63 (90%) patients were given oral calcium and vitamin D, and 7 (10%) were given intravenous bisphosphonates and oral vitamin D. Among the patients followed, 60 (85.7%) had good treatment adherence, and no side effects related to the treatment were observed in any of the patients.

Before treatment, the average vertebral DXA z-score was -3.06±1.05. Significant improvement was observed when comparing pre-treatment with the first year of treatment, pre-treatment with the second year of treatment, and the first year of treatment with the second year of treatment ($p<0.05$). A significant increase in 25(OH)D levels was observed when comparing pre-treatment with the first year of treatment and pre-treatment with the second year of treatment ($p<0.05$). No significant changes were detected in serum Ca, P, ALP, PTH, and urine Ca/Creatinine values (Table 1).

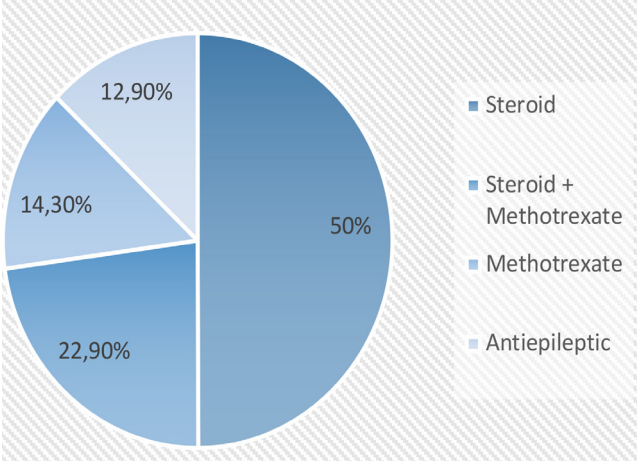

Figure 3. History of drug use among patients

Among the seven patients undergoing intravenous bisphosphonate treatment, two (28.6%) were found to have oncological diseases, two (28.6%) had rheumatological diseases, one (14.3%) had a neurological disease, and two (28.6%) had other diseases. Four patients (57.1%) had a history of steroid use, two (28.6%) had a history of antiepileptic drug use, and one (14.3%) had a history of both steroid and methotrexate use. The average duration of medication use was 3.65±1.29 years. At the time of admission, five patients (71.4%) had fractures, while two (28.6%) did not. In the pre-treatment MRI evaluations of the two patients without fractures, vertebral compression fractures were present. The average age at diagnosis of the primary disease was 4.34±3.71 years. The average time to develop osteoporosis after receiving a chronic disease diagnosis was 3.82±5.42 years. At admission, five patients (71.4%) reported various complaints such as back pain, generalized bone pain, and pain in the lower extremities, while two patients (28.6%) had no complaints. Compared to pre-treatment, there was a significant improvement in the average vertebral DXA Z score at the 1st year and 2nd year (respectively -4.19±1.15; -3.16±1.54; -2.27±1.56, $p<0.05$).

Table 1. Comparison of laboratory and imaging data before treatment, and at the 1st and 2nd years of treatment

	Before treatment	The first year of treatment	The second year of treatment	p-value
Vertebral DXA Z score	-3.06±1.05[a]	-2.51±1.09[b]	-2.16±1.15	**<0.001**
Ca (mg/dL)	9.48±0.64	9.60±0.46	9.72±0.43	0.019
P (mg/dL)	4.61±0.77	4.65±0.65	4.48±0.71	0.39
ALP (U/L)	189.3±89.88	202.1±92.52	221.1±170.11	0.322
PTH (ng/L)	53.87±33.94	46.93±20.15	38.09±19.15	0.021
25(OH)D (µg/L)	24.03±17.4[c]	42.18±130.17	27.24±9.68	**<0.001**
Urinary Ca/Kreatinine (mg/mg)	0.15±0.19	0.11±0.16	0.14±0.18	0.465

The values are presented as mean ± SD. DXA: Dual X-ray absorptiometry, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxy vitamin D, a:The difference in vertebral DXA Z score between pre-treatment and the first year of treatment and between the first and second year of treatment was $p<0.05$, b: The difference in vertebral DXA Z score between the first and second year of treatment was $p<0.05$, c: The difference in 25 (OH)D levels between pre-treatment and the first year of treatment and between the first and second year of treatment was $p<0.05$
(According to the Wilcoxon test)

Discussion

The conditions most commonly associated with secondary osteoporosis include inflammatory diseases (causing malabsorption), myopathies (e.g., Duchenne muscular dystrophy), malignancies, hemoglobinopathies (e.g., thalassemia), immobilization, and hypogonadism (6,7).

In our study, oncological diseases were found to be the most common cause of secondary osteoporosis. Secondary osteoporosis stems from direct effects of malignant cells on the skeletal system, increased inflammation-related effects, and detrimental impacts of cancer treatments on bone tissue (9). In a study examining the causes of secondary osteoporosis, the frequency of malignancy was found to be 38.4% (10). Similarly, in our study, we identified the frequency of malignancy as 30%.

The second most commonly identified chronic disease in our study was rheumatological diseases. In these patients, proinflammatory cytokines, glucocorticoid use, growth retardation, delayed puberty, inactivity, and inadequate calcium and vitamin D are among the risk factors for developing osteoporosis (1). Altaş et al. (10) found the frequency of rheumatological diseases to be 17.3% in their study. In another study, the frequency of rheumatological diseases was determined to be 9.1% (11). In our own study, we found the frequency of rheumatological diseases to be 21.5%.

In our study, nephrological and hematological diseases were equally identified as causes of secondary osteoporosis, each accounting for 15.7% of cases. In these disease groups, the high frequency of solid organ and stem cell transplantation increases the risk of osteoporosis. Altaş et al. (10) reported that 6.2% of patients had chronic kidney failure and 0.3% had undergone kidney transplantation in their study. In another study, hematological disease was found to be 18.2%, while renal diseases were detected at a rate of 9.1% (11). Additionally, Sağlam et al. (12) reported a frequency of hematological disease at 24% in their study.

In our clinic, neurological diseases were identified as a cause of secondary osteoporosis at a rate of 5.7%. Risk factors contributing to the development of osteoporosis in these patients include immobilization, reduced sunlight exposure, nutritional disorders, growth retardation, delayed puberty, and anticonvulsant therapy (1). Sağlam et al. (12) reported a frequency of neurological disease at 37% in their study. In another study, the rate of neurological disease was reported as 22.7% (11).

Among the causes of medication-induced osteoporosis, steroid use is most commonly observed (13). According to the results of our study, the medications used by patients under follow-up for secondary osteoporosis were ranked in order of frequency as steroids, steroids and MTX, MTX and antiepileptics, with steroid use being the most common, consistent with the literature.

Methods employed to prevent or treat osteoporosis in children differ from those in adults, and treatment options are limited. In our study, 63 patients (90%) received oral calcium and vitamin D, while 7 patients (10%) were treated with intravenous bisphosphonate and oral vitamin D. Bisphosphonates inhibit osteoclasts and are among the most commonly used drugs for osteoporosis treatment (14). In a study, a significant improvement was reported in bone mineral density Z scores at baseline and final evaluation after intravenous bisphosphonate treatment was administered to 34.1% of patients (-3.3±1.0 and -2.4±0.9, p=0.004, respectively) (11). Intravenous and oral bisphosphonates, as confirmed in previous studies reporting the use of bisphosphonates in secondary osteoporosis, increase bone mineral density in children (15,16).

In our study, a significant increase in 25 (OH) D levels was observed when comparing pre-treatment levels with those after the first year of treatment and also when comparing pre-treatment levels with those after the second year ($p<0.05$). However, no significant difference was found between the first and second years of treatment. It was suggested that this might be related to patients' adherence being better in the first year compared to the second year.

Study Limitations

Since our study was retrospectively planned, not all risk factors that may contribute to secondary osteoporosis could be evaluated. Additionally, being a single-center study with a limited number of patients, our results may not reflect the entire population.

Conclusion

In our study, we evaluated a heterogeneous group of various chronic systemic diseases and observed significant positive changes in BMD Z-scores and clinical findings with treatment. There is limited research specifically examining the causes of secondary osteoporosis, treatment processes, DXA monitoring, fracture development, and its relationship with bone pain in pediatric patients. There is a need for prospective studies to develop diagnostic, treatment, and follow-up guidelines for patients with secondary osteoporosis and to create larger databases to guide clinical practices.

Ethics

Ethics Committee Approval: Our cases were evaluated in accordance with the Helsinki Declaration. Approval for the study was obtained from the Ethics Committee of Akdeniz University (date: 25.01.2023, approval number: 70904504/64).

Footnotes

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

Financial Disclosure: The author declared that this study received no financial support.

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