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# 파미드로네이트 치료받은 환자에서 발생한 골간단 경화성 선에 대한 장기간 추적 연구

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# Long-term Follow-up of Metaphyseal Sclerotic Lines in Children Treated with Pamidronate

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**Purpose:** Bisphosphonates are widely used for the management steroid-induced osteoporosis (SIO) in children. With the increasing use of bisphosphonates, there have been reports of abnormal radiological findings in the growing skeleton. Therefore, their use in pediatric patients remains controversial. The present study was conducted to evaluate the long-term follow-up radiographic features, particularly metaphyseal sclerotic lines, in children who receive pamidronate therapy for nephropathy.

**Methods:** Twenty-four children with nephropathy treated with oral calcium and pamidronate (mean duration, 9 months; dose, 100 mg daily), were evaluated retrospectively. All patients had SIO secondary to chronic glucocorticoid therapy for treating nephropathy. Long bone radiographic imaging was performed before treatment with pamidronate, and at follow-up, several years later. Physeal growth rates were estimated by measuring the distance that the sclerotic lines moved on the radiographs during the corresponding time intervals.

**Results:** The mean follow-up period was 138 months. Long bone radiographs showed well-defined sclerotic lines at the metaphyseal ends, progressively moving from the physeal plate to the diaphysis, in all patients. The mean rate of movement of the sclerotic line was 6.21 mm per year. In 12 patients, the lines disappeared. The mean rate of growth in height was 7.33 cm per year.

**Conclusions:** Results of long-term follow-up suggest that the metaphyseal sclerotic lines associated with pamidronate treatment tend to disappear without affecting overall skeletal growth. Bisphosphonate treatment for SIO in children with nephropathy seems to be safe, although further studies in larger number of patients are needed.

**Key words:** Pamidronate, Bisphosphonate, Steroid-induced osteoporosis, Metaphyseal sclerotic line

## Introduction

Pamidronate is a nitrogen containing bisphosphonate. Pamidronates are widely used to treat or prevent osteoporosis. It also be used in patients with low bone mineral density and increased bone fragility, resulting from the conditions including osteogenesis imperfect, malabsorption syndromes, and skeletal disorders [1]. This drug therapy has been shown to reduce bone loss in steroid-induced osteoporosis (SIO).

There are some reports about the metaphyseal sclerotic line at the ends of metaphyses in the patients who received pamidronate [1-7]. Devogelaer et al. reported that a girl with osteogenesis imperfect show large, parallel radiopaque striae in all metaphysis on x-rays of the bones in 1987 [8]. After the report, many reports showed the metaphyseal sclerotic lines present after bisphosphonate treatment in patients with osteogenesis imperfect, fibrous dysplasia of bone, steroid-induced osteoporosis, and Gaucher disease [1, 4, 8, 9]. Multiple sclerotic lines following cyclic pamidronate treatment were called 'Zebra lines [1]. Ogden et al were called the metaphyseal sclerotic line as growth arrest line. They appeared following a temporary slowdown or cessation of rapid longitudinal bone formation in the primary spongiosa and were parallel to the contours of the contiguous physis [10].

Concerns have been raised regarding the use of pamidronates in children with skeletal growth. Therefore, their use in pediatric patients remains controversial.

The present study was conducted to evaluate the long term follow-up results of radiographic features, especially metaphyseal sclerotic lines, associated with pamidronate therapy in pediatric patients with nephropathy.

## Materials and methods

A retrospective review of the charts and radiographs of twenty four children who received pamidronate therapy was carried out. We collected demographic, clinical, and radiographic data, including gender, age, height, the bone that was studied with radiographs, the diagnosis, bone mineral density (BMD) level, the band intervals and duration of therapy (Table 1). Three patients were female. Fifteen patients had nephrotic syndrome, one had Henoch-Schonlein purpura nephritis, and eight had IgA nephropathy. All patients had steroid-induced osteoporosis because they were nephropathy patients receiving long-term corticosteroid therapy in childhood. They had steroid-induced osteoporosis despite taking oral calcium and vitamin D prophylaxis since they started corticosteroid therapy. Steroid-induced osteoporosis was defined that the Z-score was less than -2.0 [11]. Patients received oral calcium and pamidronate (100 mg) daily, regardless of their body weights [4, 12]. The duration of taking the drug varied for different conditions including follow-up BMD level and clinical feature.

Long bone radiography and BMD were performed before the treatment of pamidronate, and were followed up for several years.

The physeal growth rates during administration of pamidronates were estimated by measuring the width of the sclerotic lines on the radiographs and the corresponding time intervals. The physeal growth rates after discontinuation of pamidronates were estimated by measuring the distance that the sclerotic lines move on the radiographs and the corresponding time intervals.

The radiographic method that we used had been assessed as showing 80% magnification on conventional radiographs, and measured the distance from the end of epiphysis to the proximal end of sclerotic bands. The width of band was measured the distance from the distal end to proximal end of the bone at the midline.

Statistical analysis of the data was perfomed on SPSS 18.0. The results were presented with average±standard deviation. And comparison of growth rates was performed using Bivariate correlation analysis and Wilcoxon signed rank test. $P<0.05$ was considered statistically significant.

Approval for the study was obtained from the Institutional Review Board (IRB) at Kyung Hee University Hospital.

## Results

The mean follow-up duration was 138.41±40.33

months. The mean duration that the patients received pamidronate therapy was 9.29±4.12 months.

The mean Z score of lumbar spine BMD was -5.10± 1.54 at the initiation of pamidronate treatment.

On radiography, children shows continuous zone of metaphyseal sclerosis. The sclerotic lines became the sclerotic bands in most patients with sclerotic line. The width of metaphyseal sclerotic band is corresponded with duration of pamidronate therapy (Fig. 1).

The width of band showed positive correlation with duration of pamidronate therapy (Table 2, 3. r=0.396). It means that the sclerotic bands have been formed during the administration of pamidronate. The bands at the physeal end of long bones were detected in at least 3 months after start of pamidronate therapy.

The rate of band thickening was 9.66±8.69 mm/yr, on average.

The bands progressively move away from physis into diaphysis. The rate of movement was 6.16±3.18 mm/yr, on average.

In addition, the bands tend to disappear in the course of time (Fig. 2). The bands disappeared completely in eight patients.

The change of patient's height during pamidronate therapy was 6.11±4.39 mm per a month on average. The

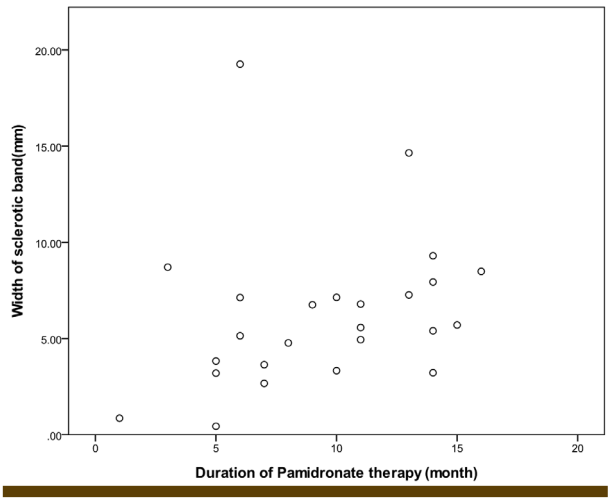


**Fig. 1.** Scatterplot of duration of pamidronate therapy and width of sclerotic band.

**Table 1.** Characteristics of 24 Patients with Metaphyseal Sclerotic Line

| No. | Sex | Age at starting pamidronate | Duration for taking pamidronate (Month) | FU period (Month) | Moving rates of sclerotic lines (mm/yr) | Thickness of bands | Growth rates during taking pamidronate (mm/mon) | Final height | Age at last follow-up |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 4 | 5 | 112 | 9.29 | 3.83 | 4.00 | 164 | 11.11 |
| 2 | M | 8 | 5 | 102 | 5.48 | 3.2 | 3.00 | 170 | 15.90 |
| 3 | F | 1 | 7 | 94 | 8.92 | 3.64 | 8.57 | 138.9 | 10.50 |
| 4 | M | 8 | 15 | 168 | 8.13 | 5.7 | 2.67 | 177 | 19.80 |
| 5 | M | 10 | 6 | 148 | 2.47 | 19.26 | 0.00 | 145 | 17.10 |
| 6 | M | 12 | 5 | 153 | 3.75 | 0.44 | 4.00 | 151.2 | 23.20 |
| 7 | M | 7 | 8 | 111 | 4.94 | 4.77 | 7.50 | 162 | 16.30 |
| 8 | M | 5 | 14 | 154 | 15.55 | 5.4 | 9.29 | 175.1 | 17.50 |
| 9 | M | 7 | 13 | 126 | 8.86 | 7.27 | 10.77 | 170 | 19.30 |
| 10 | M | 11 | 14 | 55 | 0.62 | 9.3 | 12.86 | 157 | 22.11 |
| 11 | M | 6 | 7 | 153 | 2.13 | 2.67 | 4.29 | 159 | 18.10 |
| 12 | M | 5 | 3 | 150 | 2.22 | 8.71 | 6.67 | 151.4 | 17.50 |
| 13 | F | 8 | 6 | 154 | 5.52 | 5.14 | 4.50 | 155 | 20.10 |
| 14 | M | 7 | 13 | 206 | 6.34 | 14.65 | 5.77 | 162.6 | 19.40 |
| 15 | M | 9 | 1 | 212 | 8.38 | 0.86 | 10.00 | 171.3 | 21.80 |
| 16 | M | 7 | 16 | 148 | 7.10 | 8.49 | 4.81 | 174.6 | 20.20 |
| 17 | M | 4 | 14 | 150 | 7.53 | 7.94 | 10.07 | 156.4 | 16.80 |
| 18 | F | 7 | 6 | 198 | 5.55 | 7.13 | 19.67 | 141 | 19.30 |
| 19 | M | 10 | 10 | 88 | 8.49 | 3.33 | 0.50 | 150 | 22.30 |
| 20 | M | 8 | 11 | 146 | 9.60 | 4.94 | 4.55 | 170 | 20.50 |
| 21 | M | 17 | 10 | 47 | 4.91 | 7.14 | 0.70 | 157 | 29.20 |
| 22 | M | 5 | 11 | 145 | 4.01 | 6.79 | 5.00 | 154.0 | 18.00 |
| 23 | M | 7 | 9 | 144 | 3.13 | 6.75 | 6.00 | 160.0 | 19.20 |
| 24 | M | 4 | 14 | 158 | 4.88 | 3.22 | 1.43 | 146.0 | 16.11 |

change of patient's height after pamidronate therapy was 3.73±2.32mm per a month on average.

## Discussion

Bisphosphonates are synthetic pyrophosphate analogs that have high affinity for calcium-containing crystals, concentrate preferentially in the skeleton, and affect bone surface-related processes [12]. The action of bisphosphonates involves inhibition of the mevalonate enzyme pathway in osteoclasts and binding with hydroxyapatite crystals in the bone. They exerts a direct effect by decreasing the recruitment and suppressing the function of osteoclasts, and an indirect effect by stimulationg osteoblasts to produce an inhibitor of osteoclast formation [4].

**Table 2.** Rho of Spearman about Duration of Pamidronate Therapy and width of Sclerotic Band

| | Width of sclerotic band |
|---|---|
| Duration of pamidronate therapy | r=0.396* |

*$P$<0.05

Table 3. The Rates of Growth of Long Bones and Heights

| | Mean |
|---|---|
| Rate of sclerotic band thickening (mm/year) | 9.66±8.88 |
| Rate of sclerotic band movemet (mm/year) | 6.16±3.25 |
| Growth rate during pamidronate therapy (mm/month) | 6.11±4.48 |
| Growth rate after pamidronate therapy (mm/month) | 3.73±1.35 |

Bisphosphonates suppress osteoclast-mediated bone resorption. Treatment with bisphosphonates has resulted in clinical improvement for patients with low bone mineral density and increased bone fragility. Frequency of fracture and consequent deformity were reduced. Also, pain levels are reduced, with an improvement in mobility and quality of life [1, 13-16].

Bisphosphonates have a long residence time in the skeleton and there have been concerns that long-term uninterrupted treatment may lead to accumulation of these compounds in the skeleton with a consequent suppressive action on bone metabolism. The growing bones are particularly sensitive to factors that adversely affect bone metabolism [1].

There are some reports about the metaphyseal sclerotic line at the ends of metaphyses in the patients who received paimdronate [1-7]. This sclerotic lines do not represent "frozen" bars of growth plate cartilage, but rather horizontal trabeculae undergoing turnover [3]. They are representing increased bone mineralization because of an indirect response to the inhibition of osteoclastic activity, rather than growth arrest phenomenon at the time of drug treatment.

In our study, patients receiving daily oral pamidronate

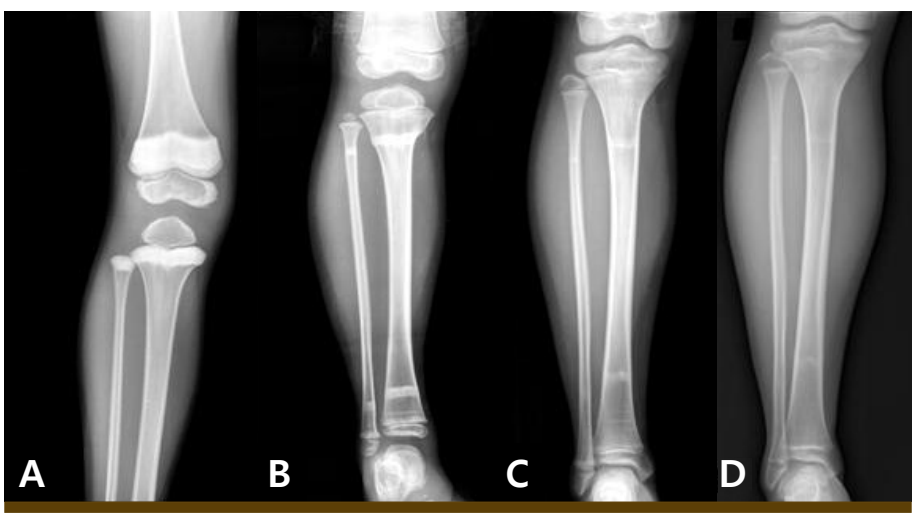


**Fig. 2.** Radiographs of the tibias were taken in a patient with pamidronate therapy for 14 momths. (A) after 5 months, (B) after 1 year, (C) after 8 years, and (D) after 10 years of treating with oral pamidronate. They shows the sclerotic band moves away from physis to diaphysis. And the band tend to disappear in the course of time.

**Table 4.** Rank Table of the Wilcoxon Signed Rank Test

| | | N | Mean Rank | Sum of Ranks | *P* |
|---|---|---|---|---|---|
| Rate of movement - Rate of thickening | Negative Ranks | 13* | 15.08 | 196.0 | 0.089 |
| | Positive Ranks | 11† | 9.45 | 104.0 | |
| | Ties | 0‡ | | | |
| | Total | 24 | | | |
| Growth rate after therapy - growth rate during therapy | Negative Ranks | 17§ | 13.59 | 231.0 | 0.021 |
| | Positive Ranks | 7‖ | 9.86 | 69.0 | |
| | Ties | 0¶ | | | |
| | Total | 24 | | | |

*Rate of movement < rate of thickening.
†Rate of movement > rate of thickening.
‡Rate of movement = rate of thickening.
§Growth rate after pamidronate therapy < Growth rate during pamidronate therapy.
‖Growth rate after pamidronate therapy > Growth rate during pamidronate therapy.
¶Growth rate after pamidronate therapy = Growth rate during pamidronate therapy.

show continuous zone of metaphyseal sclerosis corresponding the duration of treatment. It suggests that physeal growth is still occurring during the treatment.

We compare thickening rate of the sclerotic band with moving rate of the sclerotic band. There is no significant difference. It means there is no substantial deceleration in growth of long bone during treatment. The result is similar to the result in the study by Al Muderis et al [1]. We also compare the growth rate of height during treatment and the growth rate of height after treatment. 7 of 24 patients show the growth rate of height during treatment is significantly faster than that after treatment (Table 4). In some study, the linear growth in children was found to proceed normally or even better during bisphosphonate treatment, as shown in our study [17-19].

Fourteen of our patients received growth hormone therapy after pamidronate treatment. Interestingly, the patients showed higher growth rate of height during pamidronate treatment than that after pamidronate treatment. Further study to investigate the reason is needed.

In this study, the sclerotic bands gradually disappeared after termination of pamidronate treatment. It takes more than four years to disappear completely. Silverman et al. reported that growth plate calcification is found after bisphosphonate treatment for three months on radiograph. The lesion was resolved 5 months after discontinuation of treatment [20].

Limitation of our study is that the radiographs of long bone are taken with irregular intervals. We compared growth rate during treatment and after treatment despite the growth rates are different with age. It is also the limitation of our study. Prospective studies with regular follow-up radiographs are warranted.

In conclusion, the metaphyseal sclerotic lines in patients with pamidronate therapy do not disturb skeletal growth. And the sclerotic lesion moves away from physis into diaphysis, and gradually disperse.

## 한글요약

**목적:** 비스포스포네이트는 스테로이드 유발성 골다공증을 앓고 있는 환자의 치료에 널리 사용되어 왔다. 비스포스포네이트의 사용이 증가되면서 성장 중인 뼈에서 보이는 방사선학적 이상 소견에 대한 몇몇 보고가 있었다. 그래서 소아 환자에서 비스포스포네이트를 사용하는 것에 대해서는 논란의 여지가 있다. 이번 연구는 신병증을 가진 소아 환자에서 파미드로네이트 치료를 했을 때 발생한 방사선학적 이상 소견, 특히 골간단 경화성 선을 장기간 추적 관찰한 결과를 알기 위한 것이다.

**방법:** 경구로 칼슘제와 파미드로네이트(용량: 매일 100 mg)를 복용한 24명의 신병증 환아(평균 복용 기간: 9개월)를 후향적으로 연구하였다. 모든 대상 환아는 신병증에 대한 치료로 장기간 스테로이드 치료를 받았기 때문에 스테로이드 유발성 골다공증을 앓고 있었다. 파미드로네이트 치료 전에 장골의 방사선 사진을 촬영하였으며 수년간 추적 관찰 하였다. 뼈의 성장 속도는 검사를 시행한 시간 간격에 따라 방사선 사진 상에서 경화성 선이 이동한 거리를 측정하여 계산하였다.

**결과:** 평균 추적 관찰 기간은 138개월이었다. 장골의 방

사선 사진 상, 모든 환자에서 골간단의 끝부분에서 뚜렷한 경화성 선이 관찰 되었으며 이 경화성 선은 성장판에서 골간쪽으로 점점 이동하였다 경화성 선의 평균 이동 속도는 6.21 mm/년이었다. 24명 중 12명의 환자에서는 경화성 선이 완전히 사라졌다. 그리고 평균 키의 성장 속도는 7.33 cm/년이었다.

**결론:** 이번 연구에서 장기간 동안 추적 관찰한 결과 파미드로네이트 치료와 연관된 골간단부의 경화성 선은 뼈 성장에 영향을 주지 않았으며 점점 없어지는 경향을 보였다. 그러므로 신병증을 가진 소아 환자에서 스테로이드 유발성 골다공증을 비스포스포네이트로 치료하는 것은 안전한 것으로 생각된다. 그러나 좀 더 많은 수의 환자를 대상으로 하는 추가적인 연구가 필요하다.

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