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ORIGINAL ARTICLE

Development of scoliosis in young children with osteogenesis imperfecta undergoing intravenous bisphosphonate therapy

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Abstract

The purpose of this study was to clarify the prevalence of scoliosis and determine risk factors for the development of scoliosis in young children with osteogenesis imperfecta (OI) who underwent intravenous pamidronate (PAM) therapy. Thirty-four young children with OI who had no scoliosis at the first PAM administration underwent cyclic PAM therapy alone. The medical records and radiographs of these patients were retrospectively reviewed. We examined the relationship between scoliosis (Cobb angle ≥ 10) and type of OI (Sillence classification: types I, III, and IV), physical mobility, *Z*-scores of bone mineral density in L2–4 of the lumbar spine (L2–4 BMD *Z*-scores), age of patients at first treatment with PAM, pelvic frontal tilt and leg-length discrepancy. The prevalence of scoliosis was 23.5% in 34 young children with OI who underwent PAM therapy for a mean of 4.2 years. Lower L2–4 BMD *Z*-scores, the presence of coronal and sagittal vertebral deformities and higher percentage of corrective osteotomy in the lower extremities were significant risk factors for the development of scoliosis. In patients with type III or IV OI, L2–4 BMD *Z*-scores were significantly lower ($p = 0.02$) and the percentage of patients who started PAM therapy in early childhood was significantly lower in scoliosis group than in the non-scoliosis group ($p = 0.01$). Development of scoliosis depends on the severity of OI and has a strong relationship with bone fragility even under PAM therapy. Starting intravenous PAM therapy in infancy or early childhood has a potential to prevent the occurrence and progression of scoliosis associated with bone fragility in young children with severe type III or IV OI.

Keywords Osteogenesis imperfecta · Bisphosphonate · Scoliosis · Sillence classification · Pamidronate

Introduction

Osteogenesis imperfecta (OI) is an inherited bone disease caused by qualitative or quantitative defects in type I collagen, major structural component of bone, skin, and ligament, and is characterized by bone fragility and ligamentous laxity [1–3]. Sillence et al. designated four types of OI on the basis of clinical and radiographic criteria in 1979 [4], and now there are more than seven types. The most clinically relevant characteristic of OI is bone fragility, the severity of which increases in the following order: type I < IV, V, VI, and VII < III < II [3].

Spine disorder in patients with OI significantly impacts on clinical outcomes [5–7]. Spinal deformities, such as scoliosis and kyphosis, and vertebral body deformities such as flattened, biconcave, and wedged-shaped vertebrae, are often seen [2, 3, 5–7]. Respiratory difficulties secondary to spinal deformity were identified as a main cause of death [6, 7]. Study reports published before the 21st century noted that the prevalence of scoliosis in patients with OI ranged from 39 to 100% [8–16].

Bisphosphonates (BPs) are potent antiresorptive agents widely used as the mainstay of treatment for osteoporosis. Reduced fracture rates and prevention of long-bone deformities have been reported in children with OI who are given BPs [17–22]. However, there have been a few retrospective studies to elaborately investigate the effects of BP for

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the development of scoliotic deformity associated with OI [23–26] and it is still unknown whether BP therapy prevents the occurrence and progression of scoliosis in children with OI [2, 3]. There are no longitudinal studies to assess the effect of BP on patients who had no scoliosis at the time of first BP administration.

In the study we report here, we investigated the prevalence of scoliosis and sought to identify the risk factors for scoliosis in young children with OI who underwent cyclic intravenous pamidronate (PAM) therapy alone.

Materials and methods

Study participants

Our retrospective longitudinal study was approved by the ethics review boards of our institutions and was in compliance with the Helsinki Declaration. Between January 2001 and December 2014, we recruited children with OI who visited our hospitals for routine follow-up care. We identified 52 children with OI who had undergone oral BP treatment and/or intravenous PAM therapy.

Inclusion and exclusion criteria

Young children with OI who had undergone cyclic intravenous treatment with PAM alone were included in our study. All patients were treated with at least three cycle of PAM administration before puberty, and the timing and dosage of cyclic administration of PAM were adjusted with age as previously reported [27]. In brief, children under 2 years of age received 0.25 mg/kg on the first day, 0.5 mg/kg on days 2 and 3 of the first cycle, and 0.5 mg/kg daily on all 3 days in subsequent cycles. Cycles were repeated every 2 months. Children from 2 to 3 years of age received 0.38 mg/kg on the first day, 0.75 mg/kg on days 2 and 3 of the first cycle, and 0.75 mg/kg daily on all 3 days of subsequent cycles. Cycles were repeated every 3 months. In children over 3 years of age, the first 3-day cycle consisted of a 0.5 mg/kg dose on the first day and 1 mg/kg on days 2 and 3. In subsequent cycles, the dose was 1 mg/kg daily for 3 days. Cycles were repeated every 4 months.

Patients who already had scoliosis at the time of first PAM administration were excluded. Furthermore, patients who had received oral BP alone or who were started with first PAM administration after puberty were excluded. None of the patients was treated with a spinal orthosis.

Fifty-two patients with OI were enrolled in our study and 34 children with OI who were between the ages of 2 and 16 years (11 males and 23 females) met the study criteria (Fig. 1). Eight patients who had received oral BPs and 10 patients with the Cobb angle ≥ 10° at first PAM administration were excluded (Fig. 1).

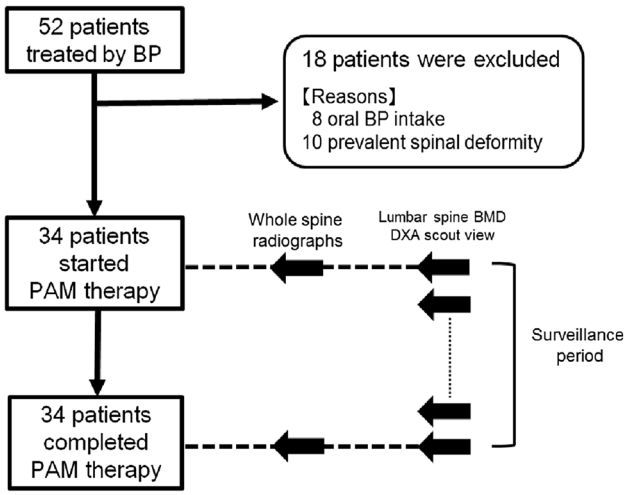

Fig. 1 Study design and disposition of subjects. *BMD* bone mineral density, *BP* bisphosphonate, *DXA* dual-energy X-ray absorptiometry, *PAM* pamidronate

Radiological assessment

The surveillance period was set from the time of first PAM administration to the latest time of administration. Frontal and lateral whole-spine radiographs in a standing or sitting position were obtained from the time of first PAM administration to the latest time of administration (Fig. 2a, b). The magnitude of scoliosis was measured and scoliosis was defined as a Cobb angle ≥ 10°. The presence or absence of vertebral deformity in the coronal and sagittal planes occurring subsequent to vertebral fractures was also assessed, and the number of the total fourteen vertebral bodies (T4–L5) that were deformed was recorded. The pelvic frontal obliquity angle was measured as an angle between the line joining the highest points of two iliac crests and the horizontal line. The leg-length discrepancy was measured using whole-leg radiographs.

Dual-energy X-ray absorptiometry [(DXA) Discovery A; Software ver12.4, Hologic, Inc., Waltham, MA, USA] was repetitively performed for all patients as a routine follow-up (every 3–4 months). Areal bone mineral density (BMD) of the lumbar spine (L2–4) was assessed by DXA, and L2–4 BMD values were converted to L2–4 BMD *Z*-scores using a standard value commonly used for Japanese children (available only in Japanese). To assess scoliosis and vertebral deformity over time, we used the scout view during DXA scans with patients in a supine position. We gauged lumbar curvature between L1 and L4 (L1–4 Cobb angle), measuring digitally on a flat monitor using built-in imaging software (Fig. 2c) [28]. As was done for whole-spine radiographs,

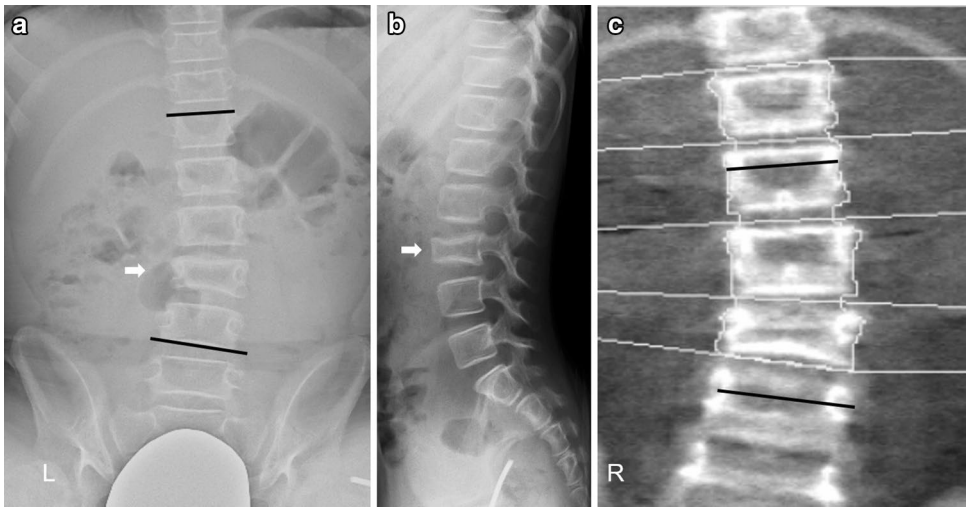

Fig. 2 Images of an 8-year-old girl with Sillence type III osteogenesis imperfecta, Gross Motor Function Classification System level 5. Pamidronate (PAM) was first administered when the child was 3 years of age, and the total number of PAM doses was 14. **a** A frontal whole-spine radiograph with the patient sitting: T12–L4 Cobb angle, 17°. A deformed L3 vertebral body is apparent in the coronal plane (arrow). **b** A lateral whole-spine radiograph with the patient sitting showed an L3 biconcave vertebral deformity. **c** The scout view on a DXA scan with the patient in the supine position provided the following data: L1–4 Cobb angle, 18°; L2–4 BMD *Z*-score, –3.1

scoliosis was also defined as a Cobb angle ≥ 10°. The scout view on DXA scans was also used to ascertain the presence or absence of vertebral deformity in the coronal plane (Fig. 2c). All radiographic measurements were performed by one observer (S. K.).

Clinical assessment

We reviewed the medical records of patients in whom OI had been diagnosed, recording age, body mass index, type of OI (Sillence type I–IV) [4], patients' age at first PAM administration, the duration and number of PAM administration, patients' physical capability, and the presence or absence of corrective osteotomy in the lower extremities. Physical capability was categorized using the five-grade Gross Motor Function Classification System (GMFCS) [29]. Patients were divided into two subgroups (a group with Sillence classification type I and a group with Sillence classification type III or IV) [30] (Fig. 3). Various demographic and radiographic parameters were analyzed between the scoliosis group (Cobb angle ≥ 10°) and the non-scoliosis group (Cobb angle < 10°).

Statistical analysis

All data were expressed here as means or mean ± SD (range) or means (95% confidential interval). Probability values of < 0.05 were considered to indicate statistical significance. We performed statistical analyses with JMP software (version 12.2.0; SAS Institute Inc., Cary, NC, USA). Comparisons of continuous variables between groups were performed using Mann–Whitney *U* test, and comparisons of nominal variables between groups were performed using the Chi square test and Fisher exact test.

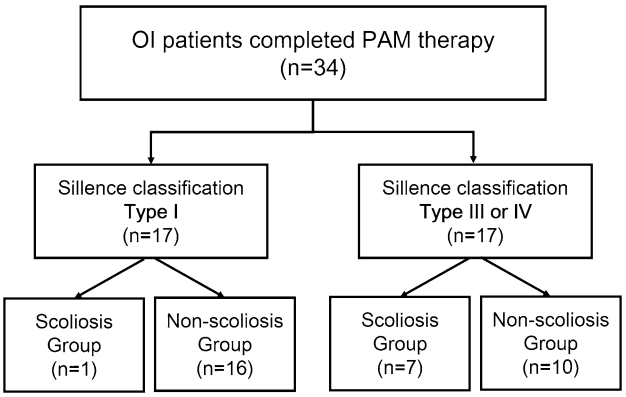

Fig. 3 Sub-grouping by the Sillence classification and the presence or absence of scoliosis

Results

Prevalence of scoliosis and vertebral deformities

Table 1 shows the characteristics of all 34 patients with OI. Whole-spine radiographs revealed eight patients (all females) had scoliosis (Cobb angle ≥ 10°) under cyclic PAM therapy. Five patients had a double curve and the other 3 patients had a single curve (a lumbar single-curve and two thoracolumbar curves). Among the 7 patients with scoliosis,

Table 1 Univariate analysis of characteristics of patients with OI receiving intravenous PAM administration: with scoliosis versus without scoliosis

Characteristic	Total ($n=34$)	Scoliosis ($n=8$)	Non-scoliosis ($n=26$)	p Value
Age at the latest PAM administration (years)	8.7 (7.2–10.1)	10.9 (6.9–14.9)	8.0 (6.4–9.5)	0.17
Sex (male: female)	11:23	0:8	11:15	0.04*
Body mass index (kg/m^2)	17.3 (16.1–18.4)	18.2 (13.1–23.2)	17.0 (16.1–17.9)	0.34
Age (years) at first PAM administration	4.4 (3.2–5.7)	5.4 (1.8–9.1)	4.1 (2.8–5.5)	0.42
Percentage of patients who started PAM therapy before the age of 6 years	67.6	50.0	73.1	0.39
Duration (years) of PAM therapy	4.2 (3.3–5.0)	5.4 (3.4–7.5)	3.8 (2.8–4.7)	0.06
Number of PAM administration	10.5 (8.4–12.6)	13.5 (9.2–17.8)	9.6 (7.2–11.9)	0.10
L2–4 BMD Z-scores	−2.2 (−3.0 to −1.4)	−4.0 (−5.6 to −2.5)	−1.5 (−2.3 to −0.8)	0.005*
Sillence classification	Type I: 17 Type III: 15 Type IV: 2	Type I: 1 Type III: 6 Type IV: 1	Type I: 16 Type III: 9 Type IV: 1	0.04*
GMFCS	Level 1: 20 Level 4: 3 Level 5: 11	Level 1:2 Level 5:6	Level 1:18 Level 4:3 Level 5:5	–
Percentage of corrective osteotomy in the lower extremities	35.3	75.0	23.1	0.01*
Percentage of patients who had deformed vertebral bodies in the coronal plane (T4–L5)	11.8	37.5	2.9	0.03*
Percentage of patients who had deformed vertebral bodies in the sagittal plane (T4–L5)	17.7	50.0	7.7	0.02*
Pelvic frontal obliquity angle (°)	1.9 (0.2–3.6)	4.8 (−4.1 to 13.8)	1.1 (0.3–2.0)	0.14
Leg-length discrepancy (mm)	5.6 (1.3–10.0)	15.7 (−6.0 to 37.3)	2.91 (0.81–5.01)	0.11

Values are means (95% confidential interval)

BMD bone mineral density, *GMFCS* Gross Motor Function Classification System, *PAM* pamidronate

*Probability values of <0.05 were considered to indicate statistical significance

there were 5 deformed vertebral bodies in the coronal plane in 3 patients (T12 [1], L1 [1], L2 [1], L3 [1], L5 [1]), and 7 biconcave vertebral bodies in 4 patients (T12 [2], L1 [2], L2 [1], L3 [1], L5 [1]). No patients had more than 6 biconcave vertebral body deformities occurring subsequent to vertebral fracture.

Risk factors for scoliosis under PAM therapy

Results of univariate analysis between the scoliosis group and the non-scoliosis group are shown in Table 1. The percentage of patients with type III OI in the scoliosis group was significantly higher than in the non-scoliosis group ($p=0.04$), and the percentage of patients who had deformed vertebral bodies in the coronal and sagittal plane and the percentage of patients with corrective osteotomy in the lower extremities was significantly higher in the scoliosis group ($p<0.05$). L2–4 BMD Z-scores were significantly lower in the scoliosis group ($p=0.005$). These results indicated that severe type OI with bone fragility is a significant risk factor for scoliosis even under PAM therapy.

The comparison between the two subgroup (Sillence classification type I versus III or IV type) revealed that the followings are statistically significant in the group with types III or IV: lower L2–4 BMD Z-scores, higher percentage of corrective osteotomy in the lower extremities, greater leg-length discrepancy, greater pelvic frontal obliquity angle, higher percentage of scoliosis and longer duration of PAM administration (Table 2).

Risk factors for scoliosis in patients with type III and IV OI

In this study, the prevalence of scoliosis was 41.1% in 17 patients with types III or IV, significantly higher than in 17 patients with type I (5.9%; $p=0.03$) (Table 2). In patients with severe type III or IV OI, patients of the scoliosis group had significantly lower L2–4 BMD Z-scores than patients of the non-scoliosis group ($p=0.02$) (Table 3). The percentages of patients who started PAM therapy before age 6 years were statistically lower in the scoliosis group ($p=0.01$), and patients who started PAM therapy before age 6 years had higher L2–4 BMD Z-scores (mean L2–4 BMD Z-scores; <6 years: -3.5, ≥ 6 years: -4.6, $p=0.18$).

Using the scout view during DXA, time-dependent changes in the L1–4 Cobb angle and L2–4 BMD Z-scores were investigated in 8 patients with scoliosis. PAM therapy improved L2–4 BMD Z-scores over time in all patients, but

Table 2 Univariate analysis of characteristics of patients with OI receiving intravenous PAM therapy: Sillence classification type I versus type III or IV

	Sillence classification type I ($n=17$)	Sillence classification type III or IV ($n=17$)	p Value
Sillence classification	Type I: 17	Type III: 15 Type IV: 2	
Age (years)	8.5 (6.5–10.4)	8.9 (6.4–11.3)	0.90
Sex (male: female)	9:8	2:15	0.03*
Body mass index (kg/m^2)	16.6 (15.5–17.7)	18.0 (15.8–20.1)	0.50
Age (years) at first PAM administration	5.3 (3.5–7.0)	3.6 (1.7–5.5)	0.12
Percentage of patients who started PAM administration before the age of 6 years	58.8	76.5	0.46
Duration (years) of PAM administration	3.1 (2.1–4.1)	5.2 (4.0–6.5)	0.01*
Number of PAM administration	7.4 (4.6–10.2)	13.6 (11.2–16.0)	0.001*
L2–4 BMD Z-scores	−0.9 (–1.6 to −0.2)	−3.5 (–4.5 to −2.5)	<0.001*
GMFCS	Level 1:14 Level 4:2 Level 5:1	Level 1:6 Level 4:1 Level 5:10	0.004*
Percentage of corrective osteotomy in the lower extremities	5.9	64.7	<0.001*
Percentage of scoliosis measured by whole-spine XP	5.9	41.1	0.03*
Number of deformed vertebral bodies in the sagittal plane (T4–L5)	0 bodies in 0 cases/238 bodies in 17 cases	6 bodies in 4 cases/238 bodies in 17 cases	0.10
Number of deformed vertebral bodies in the coronal plane (T4–L5)	1 bodies in 1 cases/238 bodies in 17 cases	11 bodies in 5 cases/238 bodies in 17 cases	0.18
Pelvic frontal obliquity angle (°)	0.5 (0.1–1.0)	3.6 (0.2–7.2)	0.01*
Leg-length discrepancy (mm)	1.1 (0.1–2.8)	11.2 (2.0–19.7)	0.006*

Values are means (95% confidential interval)

BMD bone mineral density, *GMFCS* Gross Motor Function Classification System, *PAM* pamidronate, *XP* radiographs

*Probability values of <0.05 were considered to indicate statistical significance

Table 3 Univariate analysis of characteristics of patients with Sillence type III or IV OI with scoliosis versus those without scoliosis

Characteristic	Scoliosis ($n=7$)	Non-scoliosis ($n=10$)	p value
Age (years)	11.3 (6.6–16.0)	7.2 (4.4–9.9)	0.07
Sex (male: female)	0:7	2:8	0.50
Body mass index (kg/m^2)	18.6 (12.8–24.5)	17.5 (16.0–19.0)	0.55
Age (years) at first PAM administration	5.4 (2.6–8.2)	2.4 (0.1–4.7)	0.06
Percentage of patients who started PAM administration before the age of 6 years	42.9	100	0.01*
Duration (years) of PAM administration	5.9 (3.8–7.9)	4.8 (2.9–6.6)	0.18
Number of PAM administration	14.0 (9.0–19.0)	13.3 (10.1–16.5)	0.66
L2–4 BMD Z-scores	−4.8 (–5.8 to −2.3)	−2.9 (−5.2 to −2.1)	0.02*
Number of deformed vertebral bodies in the coronal plane (T4–L5)	4 bodies in 3 cases/98 bodies in 7 cases	1 body in 1 case/140 bodies in 10 cases	0.21
Number of deformed vertebral bodies in the sagittal plane (T4–L5)	7 bodies in 4 cases/98 bodies in 7 cases	4 bodies in 1 case/140 bodies in 10 cases	0.10
Percentage of corrective osteotomy in the lower extremities	85.7	50	0.30
Pelvic frontal obliquity angle (°)	5.8 (−5.6 to 17.2)	2.3 (0.0–4.5)	0.55
Leg-length discrepancy (mm)	21.4 (2.7–45.3)	5.9 (1.0–10.8)	0.42

Values are means (95% confidential interval)

BMD bone mineral density, *PAM* pamidronate

*Probability values of <0.05 were considered to indicate statistical significance

scoliosis progressed as children aged. There were two types of scoliosis progression: In one type, sudden occurrence and acute progression were triggered by the occurrence of vertebral fracture and residual vertebral body deformity in the coronal plane (Fig. 4a). Of the 5 patients with this type of scoliosis progression, all 5 had type III OI. Furthermore, local scoliosis induced by vertebral fracture and residual vertebral body deformity in the coronal plane never regain. In the other type, scoliosis progression was gradual (Fig. 4b). Of other 3 patients with the second type of scoliosis progression, 1 had type I OI and 2 had type III OI.

Discussion

This study is the first retrospective longitudinal study to assess the effect on BP for patients who had no scoliosis at the time of first BP administration. This study showed that the development of scoliosis depends on the severity of OI and has a strong relationship with bone fragility even under PAM therapy. Intravenous PAM therapy leads to improve vertebral fragility, and starting intravenous PAM therapy in infancy or early childhood has a potential to prevent the incidence of occurrence and progression of scoliosis in young children with severe type OI.

Patients with severe type III or IV OI have a higher prevalence of scoliosis [11, 30], and the prevalence of scoliosis in 17 patients with type III or IV was significantly higher than those in 17 patients with type I (5.9%) in this study. Therefore, whether BP therapy changes the prevalence of scoliosis should be discussed in patients with severe type OI.

This study showed the development of scoliosis strongly associated with bone fragility even under cyclic PAM therapy. So far, several factors, such as fragility of vertebral bodies, damage to vertebral endplates, abnormal mobility of intervertebral joints and vertebral discs, leg-length discrepancy, pelvic frontal tilt and later achievement of anti-gravity motor milestones, have been reported to be causal factors of scoliosis in patients with OI [12, 13, 16]. Many authors reported the high prevalence of scoliosis in patients with severe type OI not treated with BP [8–16]. Engelbert et al. reported that the prevalence of scoliosis (39 children with types III or IV, mean age: 8.0 years) was 67%, and a low BMD *Z*-score is a risk factor for occurrence and progression of scoliosis [16]. Ishikawa et al. reported that the prevalence of scoliosis was 68% and that all patients with severe scoliosis (a Cobb angle of > 50°) had more than six biconcave vertebral deformities subsequent to vertebral fractures before menarche [13]. In this study, the prevalence of scoliosis in patients with type III or IV OI treated by PAM therapy alone was 41%. Patients of the non-scoliosis group with type III or IV OI had a significantly higher L2–4 BMD *Z*-score and no patients had more than 6 biconcave vertebral body deformities occurring subsequent to vertebral fracture. These results suggest that the lower prevalence of scoliosis compared with previous studies could be related with the decrease in bone fragility due to BP therapy.

Corrective osteotomy and leg-length discrepancy also modulate the development of scoliosis under cyclic PAM therapy. In this study, the non-scoliosis group had a significantly lower percentage of corrective osteotomy in the lower extremities. Patients with type III or IV OI had a significantly higher percentage of corrective osteotomy and a significantly greater leg-length discrepancy. Watanabe et al. reported that there were significant positive correlations between the extent of scoliosis and leg-length discrepancy

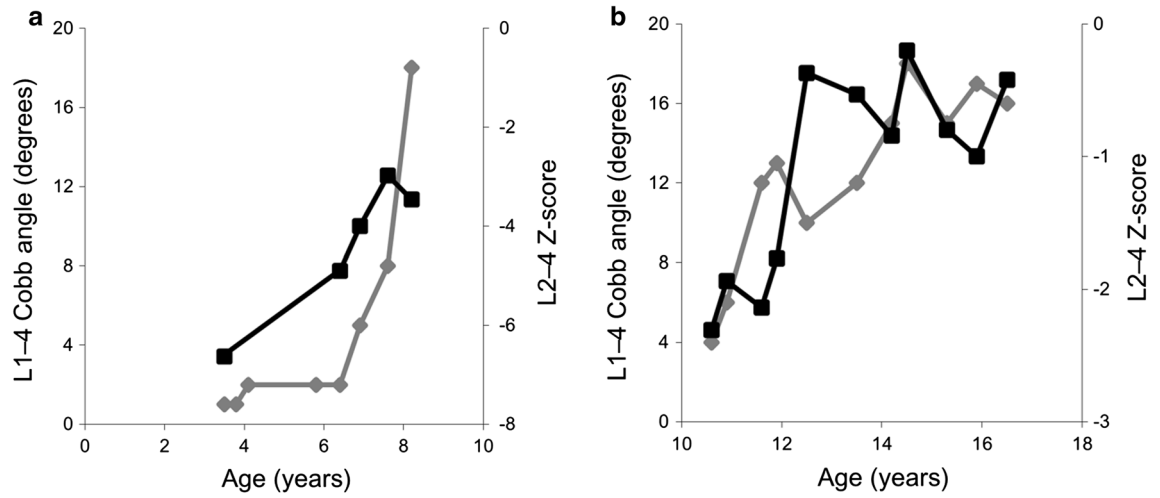

Fig. 4 Time-dependent changes in the L1–4 Cobb angle and L2–4 BMD *Z*-scores in patients with scoliosis (diamond; L1–4 Cobb angle, square; L2–4 BMD *Z*-score). There were two types for progression of scoliosis. **a** Sudden occurrence and acute progression of scoliosis deformities triggered by the occurrence of vertebral body deformity. **b** Gradual progression of scoliosis with less relation to bone fragility

[23]. Their result is consistent with our findings. Many times corrective osteotomy for long-bone deformity after fracture correlates with a greater leg-length discrepancy and frontal pelvic tilt, and can develop scoliosis in compensation for pelvic tilt. Lower incidence of corrective osteotomy in the lower extremities reflects the improvement in bone fragility due to BP therapy and may be related to the lower prevalence of scoliosis.

Only four studies have investigated the prevalence of scoliosis in patients with OI receiving BP therapy (Table 4) [23–26]. Patel et al. reported that the prevalence of scoliosis was 37.6% in 247 patients (mean age 11.8 years) with type III or IV OI treated by oral or intravenous administration of BPs [24]. However, all patients did not receive BP therapy in their study. Palomo et al. reported clinical outcomes of long-term BP therapy, and 29 of 37 patients with severe type OI (78%) had some degree of scoliosis [26]. They showed that BP therapy was associated with higher *Z*-scores of lumbar spine and fewer number of vertebral compression fractures [26]. However, due to the high prevalence of scoliosis even under BP therapy, they argued that soft tissues such as abnormal mobility of intervertebral joints and vertebral discs have a strong influence on the development of scoliosis [26]. Our results partially corroborate their findings of higher *Z*-scores of lumbar spine and fewer numbers of vertebral fractures in the sagittal plane in patients with severe type OI, but the prevalence of scoliosis is different. This difference may be derived from the differences of follow-up periods, the percentage of children after puberty and the presence or absence of scoliosis at the time of first BP administration.

It is well known that fractured vertebral bodies regain normal size and shape in infants treated with BP [19, 25, 31–33], but whether the deformed vertebral shape in the coronal plane regain or not is unknown. Letocha et al. showed that OI patients under BP therapy experienced a significant increase of total vertebral area in the sagittal and coronal plane compared with controls. They suggested the possibility that the regaining of vertebral shape in the coronal plane increase resistance to scoliosis [19]. Our study using the scout view on DXA revealed that the occurrence and progression of scoliosis is triggered by vertebral fracture and residual deformity in the coronal plane. This deformity in the coronal plane never regain over time. These findings suggest that the regaining of vertebral shape in the coronal plane may be more irreversible than in the sagittal plane.

We examined whether PAM therapy from early childhood can reduce the occurrence and progression rates of scoliosis. The percentages of patients who started PAM therapy before age 6 years were statistically lower in the scoliosis group although the duration and number of PAM administration in each group were almost identical. Anissipour et al. reported that BP therapy started before the patient reaches the age of

Table 4 Comparison of current study with previous studies

References	BP therapy	Total number of patients	Sillence classification (number of patients)	Mean age (years)	Mean follow-up period after the first BP (years)	LS BMD *Z*-scores	Prevalence of scoliosis (%)	Prevalence of scoliosis at the first BP (%)
Engelbert et al. [16]	No	39	III (18) IV (21)	8.0 (at the time of study)	–	III: −5.7 IV: −4.3	III: 72 IV: 61	–
Watanabe et al. [23]	Intravenous PAM	10 (two adults were excluded)	III (10)	8.9 (at the time of study)	N/A	III: −4.3 IV: −2.3	III: 90	N/A
Patel et al. [24]	Oral or intravenous BP (BP use: 84%)	247	III (100) IV (147)	11.8 (at the time of study)	N/A	N/A	III: 47 IV: 31	N/A
Palomo et al. [25]	Intravenous PAM or ZOL	36	III (14) IV (22)	14.5 (at the time of study)	10.8	III: −3.2 IV: −2.2	III or IV: 78	N/A
Sato et al. [26]	Intravenous PAM or ZOL (BP use: > 90%)	249	III (82) IV (167)	11.8 (at the time of study)	4.6	N/A	III: 89 IV: 61	N/A
This study	Intravenous PAM	17	III (15) IV (2)	8.4 (at the last treatment)	5.2	III: −3.9 IV: −2.4	III or IV: 44	0

Values are means

III osteogenesis Imperfecta type III, *IV* osteogenesis Imperfecta type IV, *BMD* bone mineral density, *BP* bisphosphonate, *N/A* not available, *PAM* pamidronate, *ZOL* zoledronate

6 years could modulate curve progression in type III, and their result is consistent with our results [30]. They also showed that there is a linear relationship between age and Cobb angle in patients with type III from early childhood, and the mean Cobb angles at the age of 5 and 10 were about 30° and 50°, respectively [30]. The relative importance of bone fragility versus abnormal mobility of intervertebral joint and vertebral disc in the occurrence and progression of scoliosis is different in the children's growth process. Our study suggests that PAM therapy started in infancy can lead to improve vertebral fragility and prevent the occurrence of progression of scoliosis associated with bone fragility in young children with type III or IV.

Our study had several limitations. First, it was retrospective in nature and we had no control group that did not undergo PAM therapy. Many randomized placebo-controlled studies have produced strong evidence for the effectiveness of BP [18, 21, 22]. It is impossible to set up a control group of patients who did not receive BP therapy for a long time. The second limitation was the fact that the number of patients in this study was relatively small, because of the rarity of severe types OI. The third limitation was the fact the study period of 4–5 years was relatively short and the percentage of children after puberty was relatively small. Further studies with a longer study period are necessary.

Conclusion

Recent reports have advocated starting BP therapy in early childhood for children with OI prevent bony deformity that causes motility disorders [3, 33, 34]. Our study was retrospective one with no control group, but our study show that vertebral bone fragility has a strong relationship with development of scoliosis even under intravenous PAM therapy, and starting BP therapy in infancy or early childhood has a potential to prevent the occurrence and progression of scoliosis associated with bone fragility in young children with severe types III or IV OI.

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Compliance with ethical standards

Conflict of interest None of the authors has any financial interest with any of the commercial entities mentioned in this article.

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