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Scoliosis in osteogenesis imperfecta caused by *COL1A1/COL1A2* mutations — genotype–phenotype correlations and effect of bisphosphonate treatment☆

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ABSTRACT

Bisphosphonates are widely used to treat children with osteogenesis imperfecta (OI), a bone fragility disorder that is most often caused by mutations in *COL1A1* or *COL1A2*. However, it is unclear whether this treatment decreases the risk of developing scoliosis. We retrospectively evaluated spine radiographs and charts of 437 patients (227 female) with OI caused by mutations in *COL1A1* or *COL1A2* and compared the relationship between scoliosis, genotype and bisphosphonate treatment history. At the last follow-up (mean age 11.9 [SD: 5.9] years), 242 (55%) patients had scoliosis. The prevalence of scoliosis was highest in OI type III (89%), followed by OI type IV (61%) and OI type I (36%). Moderate to severe scoliosis (Cobb angle ≥25°) was rare in individuals with *COL1A1* haploinsufficiency mutations but was present in about two fifth of patients with triple helical glycine substitutions or C-propeptide mutations. During the first 2 to 4 years of bisphosphonate therapy, patients with OI type III had lower Cobb angle progression rates than before bisphosphonate treatment, whereas in OI types I and IV bisphosphonate treatment was not associated with a change in Cobb angle progression rates. At skeletal maturity, the prevalence of scoliosis (Cobb angle >10°) was similar in patients who had started bisphosphonate treatment early in life (before 5.0 years of age) and in patients who had started therapy later (after the age of 10.0 years) or had never received bisphosphonate therapy. Bisphosphonate treatment decreased progression rate of scoliosis in OI type III but there was no evidence of a positive effect on scoliosis in OI types I and IV. The prevalence of scoliosis at maturity was not influenced by the bisphosphonate treatment history in any OI type.

1. Introduction

Osteogenesis imperfecta (OI) is a rare genetic disorder that is typically characterized by bone fragility, low bone mass and short stature. OI is usually caused by defects in one of the two genes that code for collagen type I alpha chains, *COL1A1* and *COL1A2*, even though mutations in more than 10 other genes can also lead to OI [1]. OI caused by mutations in *COL1A1* or *COL1A2* is classified into four clinical types. OI type I is the most common form of the disorder and is characterized by relatively mild bone fragility and minimal bone deformities. OI type II is lethal in the perinatal period. OI type III is a severe form of OI, with fractures at birth, multiple bone deformities, triangular face, dentinogenesis imperfecta, and extremely short stature. In OI type IV, bone fragility is intermediate between OI type I and III and there is clinical diversity of bone deformities and short stature.

Even though there is presently no causative treatment of OI, therapy with intravenous bisphosphonates is widely used to improve the skeletal symptoms of the disorder. Many studies on various bisphosphonate compounds have found that therapy in children with OI leads to an increase in bone density, decreased fracture rate and reshaping of compressed vertebral bodies [2–4].

Scoliosis is frequent in OI [5–11], and can lead to pain, a decrease in functional status and respiratory issues, which in turn are a major cause of death in severe forms of OI [9,12]. It is presently not clear whether bisphosphonate therapy prevents the development of scoliosis in children with OI. Anissipour et al. examined 316 children, adolescents and young adults with a clinical diagnosis of OI and found that 157 individuals had scoliosis, corresponding to a prevalence 50% [10]. These authors suggested that bisphosphonate treatment decreased the rate of progression of scoliosis only in children with OI type III and only if they started therapy before the age of six years. However, in that study the diagnosis of OI was not confirmed by genetic testing, which may have resulted in a genetically somewhat heterogeneous study population.

In the present study we evaluated scoliosis in 437 patients with OI types I, III and IV who all had dominant forms of OI, as confirmed by

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sequence analysis of the *COL1A1* and *COL1A2* genes. The main aim of the study was to assess the effect of intravenous bisphosphonate therapy on the development of scoliosis.

2. Materials and methods

2.1. Study population

The study population comprised individuals with a diagnosis of OI who were followed at the Shriners Hospital for Children in Montreal. Data were obtained by retrospective chart review. The study was approved by the Institutional Review Board of McGill University. As this study was a retrospective chart review, informed consent was not required. The following criteria were used to identify data sets for the present study: (i) availability of at least one spine radiograph; (ii) presence of a disease-causing heterozygous mutation in either *COL1A1* or *COL1A2*.

Spine radiographs were available from 565 patients with a clinical diagnosis of OI who had been evaluated between 1984 and 2014. In 437 of these patients, a mutation in *COL1A1* or *COL1A2* was documented. Patients had a clinical diagnosis of OI type I, III or IV (modified Sillence classification) [13,14], following an assessment by one of the authors (FHG or FR). For two patients (OI type III, N = 1; OI type IV, N = 1) spine radiographs were available only after spinal fusion surgery. Data from these two individuals were excluded from the analysis of the progression of scoliosis. In the remaining 435 patients, antero-posterior and/or lateral radiographs from a total of 1567 time points were available (OI type I, N = 464; OI type III, N = 436; OI type IV, N = 667).

2.2. Treatment

Intravenous bisphosphonate therapy consisted of infusions with pamidronate (PAM) or zoledronic acid (ZOL). Exclusively PAM was given until the year 2003. In the subsequent years, we increasingly used ZOL. PAM was administered by intravenous infusion over a 4-hour period, on each of three successive days, as described [14]. The initial annual dose of pamidronate was 9 mg per kg body weight ('full-dose PAM'). ZOL infusions were administered over 45 min at a single dose of 0.05 mg per kg body weight, repeated every 6 months. Thus, the annual dose of ZOL was 0.1 mg per kg body weight ('full-dose ZOL'). Treatment was interrupted for at least 4 months after orthopedic interventions involving osteotomies or spine fusion, in order to facilitate bone healing [15]. The bisphosphonate treatment schedule was not altered after fractures, as our previous studies had not shown an effect of pamidronate on bone healing after fractures [16]. Bisphosphonate infusions were discontinued once longitudinal growth had ceased.

Bisphosphonate treatment was recommended for all patients with OI types III and IV, as well as those patients with OI type I who had a history of significant vertebral or long-bone fractures, as described elsewhere [14]. Nevertheless, some families decided to have bisphosphonate treatment administered at other institutions. Consequently, some patients for whom bisphosphonate treatment was recommended did not have radiographic follow-up at our institution after this treatment was started.

2.3. Evaluation of spine radiographs

Spine radiographs were obtained in standing position when possible and otherwise in the sitting position. Scoliosis was said to be present when a Cobb angle of ≥10° was observed [17]. Moderate scoliosis was defined as a Cobb angle of ≥25 and <50°. Severe scoliosis was defined as a Cobb angle of ≥50° or a history of spinal fusion surgery. The number of curves (single, double, or triple) was evaluated and the Cobb angle and side convexity (right or left) were determined. In double or triple curve the maximum Cobb angle was used for analysis. Serial annual x-rays were reviewed when available to establish rates of change in Cobb angle. Patient initiation of bisphosphonate treatment was recorded and curve progression quantified before bisphosphonate treatment and during bisphosphonate treatment.

2.4. Collagen Type I mutation analysis

Sequence analyses of *COL1A1* and *COL1A2* were performed in genomic DNA, either by Sanger sequencing (Applied Biosystems 3100 DNA sequencer) after PCR amplification of all exons of *COL1A1* and *COL1A2*, or by semiconductor-based next-generation sequencing using an Ion Torrent PGM device (Life Technologies), as described [18]. Results were compared to RefSeq sequences NM_000088.3 for *COL1A1* and NM_000089.3 for *COL1A2*. As per study design, all individuals included in the present study were positive for a disease-causing mutation in *COL1A1* or *COL1A2*.

The following genotypic groups were distinguished: Mutations in *COL1A1* that introduce stop codons or lead to frameshifts were classified as haploinsufficiency mutations. Mutations in either *COL1A1* or *COL1A2* that lead to glycine substitutions in the triple helical domains of the collagen type I alpha 1 or alpha 2 chains were regarded as glycine substitutions. Mutations close to exon/intron boundaries that were predicted or proven to affect splicing were considered splice mutations. Mutations affecting the C-propeptide of either the alpha 1 or the alpha 2 chain of collagen type I were classified as C-propeptide mutations. Other types of mutations were too rare for statistical analysis (n = 9) and therefore were excluded from the evaluation of genotype–phenotype associations.

2.5. Statistical analysis

Anthropometric measurements were converted to age- and sex-specific z-scores based on reference data reported by the Centers for Disease Control and Prevention [19]. Group differences in dichotomous variables were tested for significance using the chi-square test. Independent sample t-tests or the Mann–Whitney U-test were used to compare mean values of continuous variables, as appropriate. The difference of z-score results to 0 (i.e., the mean result expected in the general population) was tested for significance using the one sample t-test.

Differences in continuous variables between OI groups were evaluated for significance using analysis of variance (ANOVA). Bonferroni's adjustment was used to perform post-hoc comparisons. Multiple regression analysis was performed to identify the determinants of scoliosis progression in OI patients. The progression rate was used as the dependent variable, whereas age, sex, disease severity and bisphosphonate treatment status were entered as predictors. Sex was coded as follows: female = 1; male = 2. Disease severity was derived from OI types, as follows: OI type I = 1; OI type IV = 2; OI type III = 3. Treatment status was coded as follows: No prior bisphosphonate treatment = 1; during bisphosphonate treatment = 2. A 5% significance level was used throughout, and all tests were two-sided. Calculations were performed using SPSS Software Version 22 (SPSS, Inc., Chicago, IL, USA).

3. Results

Among the 437 patients who were included in the present study, OI type I was the most prevalent diagnosis, followed by OI type IV and OI type III (Table 1). About two thirds of patients had mutations in *COL1A1*, the remainder had *COL1A2* mutations. By the time of the last follow-up visit, at an average age of about 12 years, 75% of patients had received bisphosphonate treatment. Slightly more than half of the patients had scoliosis, but the prevalence of scoliosis and of spinal surgery varied markedly between OI types, as expected.

The assessment of scoliosis prevalence in different age groups (Table 2) showed that moderate to severe scoliosis (Cobb angle ≥25° or history of spinal fusion surgery) was not observed in OI type I before the age of 5.0 years and affected fewer than 20% of the patients with OI

Table 1
Clinical characteristics and prevalence of scoliosis according to clinical diagnosis at the last follow-up visit.

	All	OI Type I	OI Type III	OI Type IV	P
N (M/F)	437 (210/227)	188 (95/93)	82 (37/45)	167 (78/89)	0.65
Gene affected (*COL1A1*/*COL1A2*)	284/153	156/32	40/42	88/79	<0.001
Age (years)	11.9 (5.9)	11.9 (5.9)	12.4 (5.7)	11.5 (6.0)	0.54
Height (z-score)	−3.3 (3.0)	−1.0 (1.2)[ab]	−7.6 (2.3)[b]	−3.9 (2.1)	<0.001
History of bisphosphonate treatment (yes, N [%])	326 (75)	91 (48)	75 (92)	160 (96)	<0.001
Age at start of bisphosphonate therapy (years)	5.3 (5.0)	7.1 (4.5)[ab]	4.5 (5.3)	4.7 (5.0)	<0.001
Scoliosis (yes, N [%])	242 (55)	67 (36)	73 (89)	102 (61)	<0.001
Moderate scoliosis (yes, N [%])	66 (15)	14 (7)	23 (28)	29 (17)	<0.001
Severe scoliosis (yes, N [%])	67 (15)	3 (2)	37 (45)	27 (16)	<0.001
Spinal surgery (yes, N [%])	35 (8)	3 (2)	17 (21)	15 (9)	<0.001

Results are given as N (%) or as mean (SD). P values represent the significance of the difference between OI types as calculated by ANOVA or chi-square test. The results of post-hoc comparisons are shown as superscripts: a: significant difference to OI type III; b: significant difference to OI type IV.

type I who were 10 years or older. In contrast, about one sixth of children with OI type III already had moderate to severe scoliosis before the age of 5.0 years, and the prevalence of moderate to severe scoliosis in this group increased to more than 90% after 15.0 years of age. In OI type IV, the prevalence of moderate to severe scoliosis was about half that seen in OI type III in each age group.

Comparison between patient groups defined by genotype showed that about a third of individuals with *COL1A1* haploinsufficiency mutations had scoliosis, but that scoliosis rarely became moderate or severe in this group (Table 3). In contrast, about two fifth of patients with triple helical glycine substitutions or with C-propeptide mutations had moderate to severe scoliosis. Among patients with splice site mutations, the prevalence of moderate to severe scoliosis was intermediate between the haploinsufficiency group and the other genotype cohorts.

The effect of intravenous bisphosphonate therapy on scoliosis was first assessed by evaluating rates of Cobb angle progression. Among patients not receiving bisphosphonates, the progression rate was significantly higher in OI type III than in OI type I or IV (Table 4). In univariate analyses, there were no significant differences between Cobb angle progression rates in the pretreatment phase and during the first two to four years of intravenous bisphosphonate therapy (OI type I, $P = 0.41$, OI type III, $P = 0.15$; OI type IV, $P = 0.06$; t-tests). However, the mean Cobb angle progression rate in OI type III during bisphosphonate therapy was numerically only about half of the pretreatment value.

As these univariate analyses compared groups that differed slightly (albeit non-significantly) in sex distribution and age, we in addition used multiple regression analyses to assess the effect of bisphosphonate treatment on Cobb angle progression rate. This revealed that, in the entire study population taken together, OI severity ($P < 0.001$) but not age ($P = 0.17$), sex ($P = 0.57$) and bisphosphonate treatment status ($P = 0.37$) was positively associated with Cobb angle progression rate. However, when only the OI type III group was considered, bisphosphonate treatment status was associated with Cobb angle progression rate ($P = 0.03$), whereas the effect of age ($P = 0.81$) and sex ($P = 0.51$) remained non-significant. The equation of multiple regression was:

Cobb angle progression rate (degrees/year) = 9.4–0.04 × age (years) + 0.98 × sex (Female = 1; Male = 2) − 3.7 × treatment status (bisphosphonate treatment, no = 1; bisphosphonate treatment, yes = 2). This showed that a Cobb angle progression rate was 3.7°/year slower in patients with OI type III who were receiving bisphosphonate therapy, a result that is very similar to that of the univariate analysis shown before.

In a second analysis to study the effect of intravenous bisphosphonate treatment on scoliosis, we assessed radiographs of patients who were at least 15.0 years of age and therefore were considered to be at or close to skeletal maturity. We compared patients who had started bisphosphonate treatment early in life (before 5.0 years of age) to patients who either had started therapy later (after the age of 10.0 years) or had never received bisphosphonate therapy. No difference in the prevalence of moderate or severe scoliosis was found between these groups (Table 5).

4. Discussion

The present study investigated scoliosis in 437 individuals with OI, a larger patient group than any previous study on this topic. All patients had dominant OI due to mutations in a collagen type I encoding gene. We found that intravenous bisphosphonate therapy had an effect on the progression of scoliosis only in OI type III, which is similar to findings made by others [10]. A new observation of the present study is that slower progression of scoliosis did not translate into a discernible effect on the prevalence of moderate to severe scoliosis at maturity. Patients who started treatment early in life (before 5.0 years of age) eventually developed moderate or severe scoliosis in similar proportion as patients who started treatment during later phases of growth (≥10.0 years of age) or had not received bisphosphonates at all.

The lack of detectable effect of bisphosphonate treatment on the prevalence of scoliosis at maturity is not surprising for OI types I and IV, as it is in line with the finding that bisphosphonate therapy did not influence Cobb angle progression rates. Nevertheless, in the OI type III group one might have expected that the slower Cobb angle increase during bisphosphonate therapy resulted in a lower prevalence of scoliosis. However, it seems that even if bisphosphonate delayed the progression of scoliosis it did not eventually prevent the development of moderate or severe scoliosis.

The small or even absent effect of intravenous bisphosphonate therapy on the development of scoliosis in children with OI is somewhat disappointing. Bisphosphonate therapy invariably increases spine bone density [20,21] and, in children with vertebral compression fractures, intravenous bisphosphonate therapy frequently is associated with

Table 2
Prevalence of moderate to severe scoliosis (Cobb angle ≥25° or history of spinal fusion) in individual age groups.

	All		OI Type I		OI Type III		OI Type IV		P
Age group	N	Scoliosis	N	Scoliosis	N	Scoliosis	N	Scoliosis	
<5.0 years	203	13 (6)	64	0 (0)	53	8 (15)	86	5 (6)	0.004
5.0 to 9.9 years	228	50 (22)	79	3 (4)	57	27 (47)	92	20 (22)	<0.001
10.0 to 14.9 years	233	88 (38)	87	11 (13)	53	41 (77)	93	36 (39)	<0.001
≥15.0 years	161	74 (46)	66	11 (17)	33	30 (91)	62	33 (53)	<0.001

Results are given as N (%). P values represent the significance of the difference between OI types as calculated by chi-square test.

Table 3
Clinical characteristics and prevalence of scoliosis according to genotype at the last follow-up visit.

	Haplo-insufficiency	Alpha 1 glycine	Alpha 2 glycine	Splice	C-propeptide	P
N (M/F)	95 (48/47)	106 (56/50)	133 (62/71)	73 (29/44)	21 (10/11)	0.56
OI type (I/III/IV)	95/0/0	17/31/58	26/40/67	45/4/24	2/4/15	<0.001
Age (years)	11.5 (6.1)	11.1 (5.7)	12.7 (5.8)	12.4 (5.9)	11.0 (6.0)	0.24
Height (z-score)	−0.8 (1.1)[abcd]	−4.7 (2.5)[ce]	−4.7 (3.3)[ce]	−2.2 (2.2)[abde]	−3.6 (2.3)[ce]	<0.001
History of bisphosphonate treatment (yes, N [%])	46 (48)	89 (84)	117 (88)	48 (66)	20 (95)	<0.001
Age at start of bisphosphonate therapy (years)	7.0 (4.8)[ad]	5.0 (5.1)[e]	5.4 (5.3)[d]	5.4 (4.7)	2.9 (4.2)[be]	0.04
Scoliosis (yes, N [%])	32 (34)	70 (66)	86 (65)	38 (52)	13 (62)	<0.001
Moderate scoliosis (yes, N [%])	7 (7)	22 (21)	22 (17)	10 (14)	5 (24)	0.08
Severe scoliosis (yes, N [%])	1 (1)	24 (23)	30 (23)	5 (7)	4 (19)	<0.001
Spinal surgery (yes, N [%])	1 (1)	14 (14)	15 (11)	2 (3)	3 (21)	0.004

Results are given as N (%) or as mean (SD). P values represent the significance of the difference between genotypes as calculated by ANOVA or chi-square test. The results of post-hoc comparisons are shown as superscripts: a: significant difference to alpha 1 triple helical glycine substitution group; b: significant difference to alpha 2 triple helical glycine substitution group; c: significant difference to splice site mutation group; d: significant difference to C-propeptide mutation group; e: significant difference to haploinsufficiency mutation group.

vertebral reshaping [2–4,22]. It is intuitive to hypothesize that improvements in the shape of individual vertebra have a beneficial effect on the overall shape of the spine. Our observations therefore suggest that scoliosis in OI is to a large extent determined by soft tissues, such as perispinal ligaments and muscle pull. This explanation is in accordance with our previous observations in OI type I, where we did not find a clear relationship between vertebral compression fractures and scoliosis [23]. The importance of soft tissues in the development of scoliosis is also highlighted by the observation that scoliosis is a common complication of some genetic conditions that affect ligaments and tendons, such as Ehlers-Danlos syndrome and Marfan syndrome, but that usually are not associated with vertebral compression fractures [24,25].

Regarding genotype–phenotype correlations, we observed that 34% of patients with *COL1A1* haploinsufficiency mutations had scoliosis, which is similar to what we had previously reported in a smaller cohort of individuals with such mutations [23]. Only a small minority of patients with haploinsufficiency mutations had moderate to severe scoliosis whereas close to half of patients with glycine substitutions or C-propeptide mutations had moderate to severe scoliosis. This is in accordance with the generally more severe phenotype associated with glycine substitutions or C-propeptide mutations, as compared to haploinsufficiency mutations. Splice site mutations can lead to haploinsufficiency (if they give rise to frameshifts in *COL1A1*) or to more severe consequences such as in-frame amino acid sequence changes (if they cause exome skipping in *COL1A1* or *COL1A2*) [26]. The effect of splice site mutations on transcripts could be characterized by assessing skin fibroblasts, but such material was not available in the present study. In any case, the prevalence of scoliosis in patients with splice site mutations was intermediate between those with haploinsufficiency and those with glycine substitutions or C-propeptide mutations, which mirrors the range of outcomes of splice mutations on the molecular level.

The present study population had a mean age of 12 years at last follow-up, and included children, adolescents and young adults. Little is known about the progression of scoliosis in OI after skeletal maturity has been achieved. Data from patients with adolescent idiopathic scoliosis show that scoliosis of more than 30 to 40° tends to progress even in skeletally mature individuals [27–30]. Even though it is presently not known whether this is also true in OI, it seems prudent to continue monitoring scoliosis in patients who have curves of more than 30° also after the completion of growth.

There are some obvious limitations of this study. This is a retrospective study based on radiographs that were obtained for clinical purposes, which may have introduced bias. On a technical level, the radiographs reviewed for this study were not taken in the same manner in all patients and at all time points. Radiographic examinations of the spine were performed in standing position whenever possible, but in individuals who were unable to stand it was unavoidable to obtain the radiograph in a sitting position. This increases the variability of results, as Cobb angle measurements may vary with the position in which the radiograph was performed [31]. With regard to the assessment of bisphosphonate treatment effects on scoliosis, it is a shortcoming of the present study that this is not a placebo-controlled study and therefore there is no randomly allocated control group. Also, the present retrospective data set does not contain information about the potential consequences of scoliosis on important clinical issues such as pulmonary function, pain and quality of life.

In conclusion, this study on individuals with dominant mutations in the *COL1A1* and *COL1A2* genes found that the prevalence of scoliosis at maturity was not influenced by bisphosphonate treatment history. Other treatment modalities are therefore required to prevent scoliosis in children with OI.

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Table 4
Rate of progression in Cobb angle according to OI type and bisphosphonate treatment status.

	All	OI Type I	OI Type III	OI Type IV	P
Before bisphosphonate treatment					
N (M/F)	44 (21/23)	13 (6/7)	12 (2/10)	19 (13/6)	0.02
Age at first radiograph (years)	5.0 (4.8)	6.6 (4.0)	3.0 (4.5)	5.2 (5.2)	0.17
Duration of follow-up (years)	3.5 (2.5)	3.5 (1.8)	3.6 (3.2)	3.3 (2.6)	0.95
Progression rate (degrees/year)	2.6 (5.2)	1.7 (3.0)[a]	6.7 (7.7)[b]	0.7 (2.7)	0.004
During the first 2–4 years of bisphosphonate treatment					
N (M/F)	121 (56/65)	23 (13/10)	40 (17/23)	58 (26/32)	0.54
Age at first radiograph (years)	5.3 (5.2)	6.8 (5.3)	4.4 (4.6)	5.4 (5.4)	0.19
Duration of follow-up (years)	3.2 (0.7)	3.0 (0.8)	3.2 (0.6)	3.2 (0.6)	0.35
Progression rate (degrees/year)	2.3 (3.5)	0.9 (2.3)	3.1 (3.7)	2.2 (3.7)	0.06

Results are given as N (%) or as mean (SD). P values represent the significance of the difference between OI types as calculated by ANOVA or chi-square test. The results of post-hoc comparisons are shown as superscripts: a: significant difference to OI type III; b: significant difference to OI type IV.

Table 5
Prevalence of moderate scoliosis (Cobb Angle ≥25 but <50°) or of severe scoliosis (Cobb Angle ≥50° or history of spinal fusion surgery) in patients ≥15.0 years old, according to bisphosphonate treatment history.

	Age at start of bisphosphonate		P
	<5.0 years	≥10.0 years or never	
OI Type I			
Moderate scoliosis (yes/total N [%])	2/3 (67)	2/42 (5)	NA
Severe scoliosis (yes/total N [%])	0/3 (0)	0/42 (0)	NA
OI Type III			
Moderate scoliosis (yes/total N [%])	1/14 (7)	2/13 (15)	0.60
Severe scoliosis (yes/total N [%])	13/14 (93)	9/13 (69)	0.17
OI Type IV			
Moderate scoliosis (yes/total N [%])	7/22 (32)	7/28 (25)	0.75
Severe scoliosis (yes/total N [%])	5/22 (23)	10/28 (36)	0.37

Age is given as mean (SD). Results of prevalence rate are given as N of patients with scoliosis/N of all patients (%). P values were calculated by chi-square test or t-test, as appropriate. NA: P-value not calculated, as insufficient sample size.

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