Skeletal Clinical Characteristics of Osteogenesis Imperfecta Caused by Haploinsufficiency Mutations in COL1A1

I Mouna Ben Amor, Peter Roughley, Francis H Glorieux, and Frank Rauch
Shriners Hospital for Children and McGill University, Montreal, Quebec, Canada

ABSTRACT

COL1A1 haploinsufficiency mutations lead to the mildest form of osteogenesis imperfecta (OI), OI type I. The skeletal clinical characteristics resulting from such mutations have not been characterized in detail. In this study we assessed 86 patients (36 male, 50 female; mean age 13.3 years; range, 0.6 to 54 years) with COL1A1 haploinsufficiency mutations, of whom 70 were aged 21 years or less (“pediatric” patients). Birth history was positive for fracture or long-bone deformity in 12% of patients. The average rate of long-bone fracture (femur, tibia/fibula, humerus, radius/ulna) in pediatric patients was 0.62 fractures per year, one-half of which affected the tibia/fibula. Long-bone fracture rate was negatively associated with age and lumbar spine areal bone mineral density. Vertebral compression fractures were observed in 71% of the 58 pediatric patients who had lateral spine radiographs. The median number of vertebral fractures was higher for females (median 4; range, 0 to 14) than for males (median 1; range, 0 to 8) (p = 0.03). Lumbar spine areal bone mineral density was negatively associated with the severity of vertebral compression fractures, as reflected in the spine deformity index. Scoliosis was present in about 30% of pediatric patients but the Cobb angle was <30 degrees in all cases. The average rate of long-bone fracture was negatively associated with age and lumbar spine areal bone mineral density. Vertebral compression fractures were observed in 71% of the 58 pediatric patients who had lateral spine radiographs. The median number of vertebral fractures was higher for females (median 4; range, 0 to 14) than for males (median 1; range, 0 to 8) (p = 0.03). Lumbar spine areal bone mineral density was negatively associated with the severity of vertebral compression fractures, as reflected in the spine deformity index. Scoliosis was present in about 30% of pediatric patients but the Cobb angle was <30 degrees in all cases. The average rate of long-bone fracture was negatively associated with age and lumbar spine areal bone mineral density.

KEY WORDS: COLLAGEN TYPE I; COMPRESSION FRACTURES; HAPLOINSUFFICIENCY; SCOLIOSIS; SPINE DEFORMITY INDEX

Introduction

Osteogenesis imperfecta (OI) is a heritable bone fragility disorder that is often associated with short stature and bone deformities. Additional extraskeletal features are present to a variable degree and include blue sclerae, dentinogenesis imperfecta (DI) and hearing loss.1 The severity of the bone fragility in OI covers a wide spectrum, ranging from nearly asymptomatic individuals with a mild predisposition to fractures to perinatal lethality.1 In the large majority of cases, OI is caused by dominant mutations in either COL1A1 or COL1A2, affecting the synthesis and/or structure of type I procollagen alpha1 or alpha2 chains.2 Less frequently, OI is due to recessive mutations, many of which affect genes that are involved in the posttranslational processing and trafficking of type I procollagen.2

Because many patients with OI now routinely undergo sequence analysis for COL1A1 and COL1A2 mutations, information on genotype–phenotype correlation may be useful for the management of individual patients. However, the issue is complicated by the fact that a large number of different COL1A1/COL1A2 mutations have been found, and the functional and phenotypic consequences of many types of mutations vary widely.3 An exception to this rule are nonsense or frameshift mutations in COL1A1 that are consistently associated with an OI type I phenotype, the mildest form of OI.4 On a molecular level, nonsense or frameshift mutations in COL1A1 usually trigger nonsense-mediated mRNA decay and result in collagen type I haploinsufficiency.5 Only about one-half of the normal amount of collagen type I protein is produced, whereas the structure of the produced collagen type I protein is thought to be normal. These functional consequences of the mutation are largely independent of where in the gene the mutation occurs. Therefore, haploinsufficiency mutations are thought to have a rather homogeneous downstream effect.
Even though almost all COL1A1 haploinsufficiency mutations lead to OI type I, OI type I is not always caused by COL1A1 haploinsufficiency mutations. Indeed, the database of OI mutations currently lists more than 500 different COL1A1/COL1A2 mutations that are associated with OI type I, but only about 40% of these mutations are nonsense or frameshift mutations in COL1A1.\(^{(8)}\) Therefore, the clinically defined OI type I does not necessarily cover an identical phenotypic spectrum as a genetically defined group of patients with COL1A1 haploinsufficiency mutations.

In a previous study we had noted that patients with COL1A1 haploinsufficiency mutations on average were taller, heavier, and had higher lumbar spine areal bone mineral density (LS-aBMD) than patients with mutations affecting glycine residues in the helical region of collagen type I.\(^{(8)}\) Patients with haploinsufficiency mutations also had significantly higher cortical width and lower bone turnover parameters on iliac bone histomorphometry.\(^{(8)}\)

This previous study focused on the quantitative description of bone development in individuals with COL1A1 haploinsufficiency mutations but did not address specific clinically relevant traits such as final height, long-bone fracture rate, the number and severity of vertebral compression fractures, development of scoliosis, and intrafamilial phenotypic variability. Such data could provide useful guidance for counseling, prognosis, and timely management. In the present study we therefore analyzed the clinical features of patients with OI due to haploinsufficiency mutations in COL1A1.

Subjects and Methods

Subjects

The study cohort included all 86 patients (36 male, 50 female; mean age 13.3 years; range, 0.6 to 54 years) with known nonsense or frameshift mutations in COL1A1 who were evaluated at the Shriners Hospital for Children in Montreal between March 1992 and August 2010. All patients had a clinical diagnosis of OI type I according to the Sillence classification,\(^{(9)}\) following an assessment by one of the authors (FHG or FR). Data were obtained by retrospective chart review. The study was approved by the Shriners Hospital Institutional Review Board. Informed consents were obtained from the legal guardians and/or patients.

The availability of clinical data varied with the age of study participants. Subjects aged 21 years and lower (n = 70) were followed longitudinally, including with radiographs, as clinically indicated. Subjects above the age of 21 years (n = 16) had a single evaluation, including history, anthropometry, and lumbar spine bone densitometry, but no radiographs were obtained. Therefore, information based on radiograph is limited to subjects aged 21 years or less (“pediatric group”). The age distribution of the study cohort is shown in Fig. 1.

Collagen type I mutation analysis

Total genomic DNA was extracted from saliva or peripheral blood using standard extraction methods. All 51 exons of COL1A1 including the exon-intron boundaries were amplified by polymerase chain reaction using primers described previously.\(^{(10)}\) The sequencing reaction was performed using a BigDye Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA). The nucleotide sequence was determined using an Applied Biosystems 3100 DNA sequencer. Sequence traces were aligned with the GenBank reference sequences of the COL1A1 genomic DNA (AF017178). Mutations that were not listed in the database of OI mutations\(^{(6,7)}\) as of March 2012 were considered novel.

Anthropometry

Height and weight were converted to age-specific and sex-specific Z-scores based on reference data published by the Centers for Disease Control and Prevention.\(^{(11)}\) Final height was considered to be reached when postpubertal individuals had a height increase of less than 2 cm in 2 successive years.

Bone densitometry

Bone densitometry was performed in the anteroposterior direction at the lumbar spine (L₁–L₄) by dual-energy X-ray absorptiometry (DXA; QDR Discovery, Hologic, Inc., Waltham, MA, USA). Vertebra affected by fractures or by visible degenerative changes were excluded from analysis. LS-aBMD results were converted to age-specific and sex-specific Z-scores combining reference data from Salle and colleagues\(^{(12)}\) (for patients younger than 2 years of age) and data provided by the densitometer manufacturer. Only results obtained at the Shriners Hospital were used for analysis. For patients who had never received bisphosphonate treatment, the last available result was used for the present analysis. For patients with a history of bisphosphonate treatment, the last measurement recorded prior to the initiation of this therapy was used.

Analysis of vertebral compression fractures and scoliosis

Both anteroposterior and lateral spine radiographs were analyzed for each patient when available. Lateral spine radiographs were obtained in a supine position. For patients who had never received bisphosphonate treatment, the last available spine...
radiographs were used for the analysis. For patients with a history of bisphosphonate treatment, the last spine radiographs obtained prior to the initiation of this therapy was used. Suitable lateral spine radiographs were available from 58 patients, and anteroposterior spine radiographs were available for 52 patients.

The anteroposterior radiographs were assessed for scoliosis. Scoliosis was said to be present when a Cobb angle of >10 degrees was observed. To determine the Cobb angle, the end vertebrae of the largest scoliosis curve were selected as those with the greatest angle to the vertical axis. A line was drawn along the superior endplate of the superior end vertebra and a second line was drawn along the inferior endplate of the inferior end vertebra. The angle between these two lines is measured as the Cobb angle. The measurement was performed by a radiologist.

The lateral radiographs were evaluated for the presence or absence of vertebral compression fractures. The Genant semiquantitative method was used for vertebral fracture assessment from T3 to L4. Vertebrae bodies were assigned a severity score: Grade 0 (normal), Grade 1 (mild), Grade 2 (moderate), or Grade 3 (severe). The morphometric grading corresponds to the extent of the difference in height ratios from 100% when the anterior vertebral height was compared to the posterior height, the middle height to the posterior height, and the posterior height to the posterior heights of the adjacent vertebral bodies. The scores corresponded to the following differences in height ratios: Grade 0 = 20% or less (normal); Grade 1 fracture = >20% to 25%; Grade 2 fracture = >25% to 40%; Grade 3 fracture = >40%. Minimal physiological rounding of vertebral bodies in the mid-thoracic region of the spine, as can be seen in normal children, was assigned a Grade 0 score.

The assessment was performed by two experts in pediatric bone disorders (MBA and FR).

The spine deformity index (SDI) was determined by summing the grade of each vertebra from T3 to L4 in each patient. The SDI ranges between 0 (in the absence of compression fractures from T3 to L4) and 42 (if all vertebrae from T3 to L4 are coded as grade III). This index is useful for summarizing the number and the severity of vertebral fractures in a single metric.

**Analysis of long-bone fracture incidence**

The incidence of long-bone fractures (humerus, radius/ulna, femur, and tibia/fibula) was determined based on radiographic evidence.

For the analysis of baseline fracture incidence, only fractures that occurred without prior exposure to bisphosphonates were considered. The analysis took into account long-bone fractures that occurred during the first 2 years after the first visit to our clinic and was limited to patients who had had at least 6 months of prospective follow-up. Thus, for each patient, the observation interval ended on the day when bisphosphonate treatment was started, or, in patients who never received bisphosphonates, at the end of 2 years of observation. Using these criteria, 34 patients did not contribute to the analysis of long-bone fracture rate: 30 patients had <6 months of follow-up and 4 patients had already received bisphosphonate treatment prior to the initial evaluation in our clinic. The individual fracture rate in the remaining 52 patients was computed by dividing the total number of fractures by the length of the observation period for each patient. Fractures that involved the ulna and radius or both theibia and fibula were counted as one fracture.

Twenty-five of these 52 patients subsequently were treated with an intravenous bisphosphonate (either pamidronate or zoledronate), starting at a median age of 8.8 years (range, 1.0–18.5 years). To assess the effect of bisphosphonate treatment on long-bone fracture incidence, the individual long-bone fracture rate during bisphosphonate treatment was determined by dividing the total number of long-bone fractures by the length of the observation period for each patient.

**Statistical analysis**

Anthropometric measurements were converted to age-specific and sex-specific Z-scores based on reference data reported by the Centers for Disease Control and Prevention. Group differences in dichotomous variables were tested for significance using the chi-square test. The independent sample t test was used to compare continuous variables with normal distribution, and the Mann-Whitney U test was used for non-normally distributed variables. The long-bone fracture incidence before and during intravenous bisphosphonate treatment was compared by paired t test. Stepwise multiple regression analysis was used to assess potential predictors of long-bone fracture rate and SDI. Nominal variables were coded as follows: gender: male = 0, female = 1. Logistic regression analyses were performed to evaluate factors associated with the presence of compression fractures and scoliosis. A 5% significance level was used throughout, and all tests were two-sided. Calculations were performed using SPSS Software Version 18 for Windows (SPSS, Inc., Chicago, IL, USA).

**Results**

**Basic clinical evaluation (entire study population)**

The 86 study participants were from 53 different families and had 46 distinct mutations, 14 of which were novel (Supplementary Table 1). The family history was positive for OI type I in 63 patients, negative for OI type I in 21 patients, and not known in 2 patients.

Birth history was available for 58 patients and was positive for fracture or long-bone deformity in 7 patients (12%). The mean birth weight was 3279 g (SD = 548 g). At the last clinical follow-up (at a median age of 15 years; range, 9 months to 54 years), blue sclerae were present in 79 of the 86 (92%) patients, and dentinogenesis imperfecta was noticed on inspection in 3 of the 75 (4%) patients with documented dental findings.

Forty-two participants (49%) of the present study (18 males and 24 females) had a history of bisphosphonate treatment. The age at the start of bisphosphonate treatment ranged from 11 months to 18 years. In 16 patients, this treatment was initiated because of significant vertebral compression fractures alone. In the remaining 26 patients, bisphosphonate treatment had been started because they had both vertebral compression fractures and a history of recurrent long-bone fractures, following the treatment approaches described.

At the time of the last evaluation in the absence of bisphosphonate exposure, patients on average were mildly...
short and had nearly average weight (Table 1). The mean LS-aBMD Z-score was low, and significantly lower in males than in females, even though male patients had higher height Z-scores than female patients (Table 1).

At the time of the last follow-up examination, 42 patients had reached final height, averaging 155 cm in females (Z-score, −1.06) and 167 cm in males (Z-score, −1.14). This corresponds to a deficit of 8 cm and 10 cm, respectively, when compared to the average of the general population. Twenty of the patients who had achieved final height were positive for a history of bisphosphonate treatment, which had been started at a median age of 8 years (range, 4–18 years). The mean Z-score for final height was −1.0 (SD, 0.7) in the untreated group and −1.5 (SD, 1.5) in the group that had received bisphosphonate treatment (p = 0.18).

Radiographic and longitudinal analyses (pediatric population only)

Skull radiographs were available in 41 patients (median age, 15 years; range, 3–21 years), of whom 11 (27%) were positive for Wormian bones.

**Long-bone fractures**

Long-bone fracture rates in the absence of bisphosphonate exposure were evaluated in 48 patients (25 females, 23 males). The median age at the start of the observation period was 3.6 years (range, 10 days to 17 years), with a cumulative follow-up period of 83.9 years. During the observation period, 24 (50%) patients had at least one long-bone fracture; the total number of fractures was 49. The average long-bone fracture rate during the follow-up period was 0.62 fractures/year. The most common fracture site was tibia/fibula (n = 24; 49% of all long-bone fractures) followed by femur (n = 13; 27%), radius/ulna (n = 11; 22%), and humerus (n = 1; 2%). One femur fracture was treated by intramedullary rodding surgery, the other fractures were treated without surgery.

In the 25 patients who subsequently received intravenous bisphosphonate treatment, the average long-bone fracture rate was 0.77 fractures/year pretreatment and 0.44 fractures/year after treatment had been started (p = 0.20, paired t test).

To assess determinants of long-bone fracture rate, regression analysis was performed. None of the tested variables (gender, age, height Z-score, weight Z-score, LS-aBMD Z-score) was independently associated with annual long-bone fracture rate.

**Vertebral compression fractures**

The presence of vertebral compression fractures in the absence of prior bisphosphonate treatment could be assessed in 58 patients (27 male, 31 female; mean age, 7.4 years; range, 0.6–18 years). In 17 patients, no fracture was visible on lateral spine radiographs. In the other 41 patients (71% of the patients with sufficient data), a total of 179 vertebral fractures were recorded from T3 to L4. The most common fracture sites were T7 and T8 (Fig. 2). The proportion of individuals with vertebral compression fractures was higher in females (84%) than in males (56%) (p = 0.02 by chi-square test). The median number of vertebral fractures was two (range, 0–14). The median number of fractures was higher for females (median, 4; range, 0–14) than for males (median, 1; range, 0–13).

---

### Table 1. Numbers and Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>n (M/F)</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>86 (36/50)</td>
<td>13.3 ± 13.9</td>
<td>12.4 ± 13.1</td>
<td>14.1 ± 14.5</td>
</tr>
<tr>
<td>Height (Z-score)</td>
<td>84 (35/49)</td>
<td>−0.9 ± 1.0</td>
<td>−0.7 ± 1.0</td>
<td>−1.2 ± 1.0</td>
</tr>
<tr>
<td>Weight (Z-score)</td>
<td>84 (35/49)</td>
<td>−0.1 ± 1.4</td>
<td>0.02 ± 1.5</td>
<td>−0.3 ± 1.4</td>
</tr>
<tr>
<td>LS-aBMD (Z-score)</td>
<td>85 (35/50)</td>
<td>−3.0 ± 1.2</td>
<td>−3.4 ± 1.1</td>
<td>−2.7 ± 1.3</td>
</tr>
<tr>
<td>Final height (Z-score)</td>
<td>42 (15/27)</td>
<td>−1.0 ± 1.2</td>
<td>−1.1 ± 1.1</td>
<td>−1.1 ± 1.1</td>
</tr>
</tbody>
</table>

None of the patients had received bisphosphonate treatment at the time when these data were obtained. Data are mean ± SD. The p value indicates the significance of the difference between males and females. In the “All” group, the difference of Z-scores from 0 by one-sample t test is indicated by asterisks: *p < 0.001.

LS-aBMD = lumbar spine areal bone mineral density.

---

**Fig. 2.** Site distribution and severity of vertebral compression fractures in 41 patients with vertebral compression fractures.
(median, 1; range, 0–8) ($p = 0.03$), even though LS-aBMD Z-scores at the time of spine radiography were similar between the two genders (mean ± SD: −3.3 ± 1.1 in males versus −3.1 ± 1.1 in females; $p = 0.4$).

A logistic regression analysis was performed to determine which clinical characteristics were independently associated with the presence of compression fractures (Table 2). We found that female gender was associated with higher odds for the presence of compression fractures, whereas a higher LS-aBMD Z-score decreased the odds. Age, height Z-score, and weight Z-score were not significantly associated with the presence of compression fractures.

The previous analysis was dichotomous and only assessed whether or not at least one vertebral fracture had occurred. In order to also elucidate which parameters determined the severity of spine involvement, we performed a multiple regression analysis with SDI as the dependent variable. This revealed that female gender was associated with a higher SDI. In addition, we found that LS-aBMD Z-score was negatively and height Z-score positively associated with SDI. The regression equation was: $SDI = -1.53 + 7.5 \times (gender, male = 0, female = 1) - 4.21 \times (LS-aBMD Z-score) + 2.32 \times (height Z-score); r^2 = 0.4, p < 0.01$.

**Scoliosis**

The presence of scoliosis in the absence of prior bisphosphonate treatment could be evaluated in 52 patients (28 males, 24 females; median age: 9.6 years; range, 0.6–21 years). Fifteen of these patients (29%) had scoliosis. The Cobb angle was <30 degrees in all patients, indicating mild scoliosis. A logistic regression analysis was performed to determine the clinical characteristics associated with the presence of scoliosis. This showed that age was significantly associated with the odds of having scoliosis, whereas gender, SDI, as well as Z-scores of height, weight, and LS-aBMD were not significantly associated with the presence of scoliosis (Table 3).

**Discussion**

In this study we found that patients with OI caused by COL1A1 haploinsufficiency mutations had an 8 to 10 cm deficit in final height compared to the general population. Fractures were rare at birth, but approximately one long-bone fracture occurred every other year thereafter. Surprisingly, vertebral compression fractures were more frequent and more severe in females. A higher LS-aBMD was associated with fewer and less severe vertebral compression fractures. Less than one-third of the study population had scoliosis and, when present, scoliosis was mild.

When compared to OI caused by other types of mutations, the skeletal involvement caused by COL1A1 haploinsufficiency mutations is relatively "mild." The average final height Z-score in our patient group was −1.1, which is very similar to a study by Lund and colleagues, who reported a height Z-score of −1.3 in patients who had decreased collagen type I protein production in skin fibroblasts and therefore presumably had haploinsufficiency mutations. In comparison, we had previously observed that mutations in the triple helical domains of the COL1A1/ COL1A2 genes (leading to clinical diagnoses of OI types I, III, or IV) were associated with a median height Z-score of −4.1. The observation that patients with a history of bisphosphonate treatment had a numerically lower average final height may reflect the fact that bisphosphonate treatment was reserved for patients with more severe bone fragility, including long-bone fractures and vertebral compression fractures, which is expected to lead to lower height. We have previously shown in longitudinal analyses that intravenous pamidronate treatment of children with OI is associated with significant height gain when compared to untreated patients.

Even though the phenotype of patients with haploinsufficiency mutations may be “mild” when compared to other OI patients, the long-bone fracture rate of our study population was dramatically increased when compared to the general population. Patients in the present study had 6200 long-bone fractures per 10,000 person years. To put this number into perspective, a population-based British study on individuals <18 years of age found that the combined incidence of long-bone fractures was about 65 per 10,000 person years. Thus, patients with COL1A1 haploinsufficiency mutations have a 95-fold increased long-bone fracture risk. This is probably an underestimate, given that the fracture rate in our study reflects only the observation period that was not influenced by bisphosphonate treatment. Because patients with more fractures are more likely to receive bisphosphonate treatment, this approach may have introduced a systematic bias.

We found a nonsignificant decrease in long-bone fracture rate in the patients who started intravenous pamidronate treatment, but it must be acknowledged that such results are difficult to interpret. Intravenous pamidronate treatment is associated with

---

**Table 2. Logistic Regression Analysis for the Presence (Yes/No) of Compression Fractures in 58 Patients**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-aBMD (Z-score)</td>
<td>0.4 (0.2–0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Height (Z-score)</td>
<td>1.3 (0.6–3.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Weight (Z-score)</td>
<td>1.1 (0.6–2.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.97 (0.86–1.09)</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>6.6 (1.5–28.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; LS-aBMD = lumbar spine areal bone mineral density.

**Table 3. Logistic Regression Analysis for the Presence (Yes/No) of Scoliosis in 52 Patients**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-aBMD (Z-score)</td>
<td>0.6 (0.2–1.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Height (Z-score)</td>
<td>1.3 (0.4–3.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Weight (Z-score)</td>
<td>1.0 (0.5–2.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.32 (1.08–1.60)</td>
<td>0.005</td>
</tr>
<tr>
<td>Spine deformity index</td>
<td>0.98 (0.84–1.13)</td>
<td>0.78</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>0.5 (0.1–4.0)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; LS-aBMD = lumbar spine areal bone mineral density.
better mobility function, and more active mobility may increase the risk of accidents that lead to fracture. Thus, two positive treatment effects—increased bone density and increased mobility—may counteract each other with respect to long-bone fracture rate. The relative importance of these factors is difficult to tease out in an observational study such as the present one.

Vertebral compressions were very prevalent in patients with COL1A1 haploinsufficiency mutations. At least one vertebral compression was found in 71% of the patients who had a lateral spine X-ray. However, in the early years of the observation period, lateral spine radiographs were obtained only when vertebral fractures were suspected clinically. This focus on symptomatic patients may have led to an overestimation of vertebral fracture prevalence in this study, because patients who did not have back pain (and therefore may have been more likely to be free of vertebral fractures) were not examined radiographically and therefore were not included in the present analysis. Nevertheless, it is clear that pediatric patients with COL1A1 haploinsufficiency mutations have a high prevalence of vertebral compressions. We now perform lateral spine X-rays in such patients at least once every 2 years until growth is completed. Detecting vertebral compression fracture has important implications, as compressed vertebra can reshape when intravenous bisphosphonates are given to growing patients. The benefits of bisphosphonate treatment in adults with OI are less clear. The present study does not shed light on the incidence of vertebral fractures in adults with COL1A1 haploinsufficiency mutations and therefore does not provide a basis for recommending a specific clinical follow-up schedule in such adults.

In this cohort, vertebral fractures were strikingly more common and more severe in females, even though females had somewhat higher LS-aBMD Z-score than males. The higher bone density in females may be related to the fact that, according to our previous histomorphometric studies, bone turnover is lower in females with OI than in males. Lower bone turnover is expected to lead to slightly higher bone mass because at any one time a smaller amount of bone will have been transiently removed by remodeling. Why vertebral fractures were nevertheless more frequent and more severe in females is unclear at present. A similar gender-difference in the rate of vertebral fractures does not seem to occur in other circumstances. Other pediatric studies on vertebral fractures in the context of leukemia or rheumatic disorders and population-based studies in adults did not find a significant gender difference in the prevalence of vertebral compressions.

The predilection for vertebral fractures in the mid-thoracic region was similar to what has been consistently reported in both pediatric and adult studies, and is proposed to result from the mechanical stresses on vertebrae induced by the shape of the spine. The thoracic kyphosis is most pronounced at the mid-thoracic region so that loading in flexion is accentuated. It is noteworthy that the LS-aBMD Z-score was associated with both the incidence of long-bone fractures and the prevalence of vertebral compressions. This observation indicates that LS-aBMD provides some indication about fracture risk also in young patients with OI due to COL1A1 haploinsufficiency mutations.

Scoliosis affected about 30% of the patients in whom adequate radiographic documentation was available. As the prevalence of scoliosis is approximately 3% in the general population, the risk of scoliosis seems to be increased about 10-fold in patients with COL1A1 haploinsufficiency mutations. Authors of previous studies on scoliosis in OI have speculated that it is caused by vertebral collapse. However, in the present study we did not find a relationship between the severity of vertebral compression fractures as expressed by the SDI and the presence of scoliosis. It thus appears that at least in patients with COL1A1 haploinsufficiency mutations, factors other than vertebral fractures contribute to the development of scoliosis, such as the composition and mechanical properties of the spinal soft tissues.

One limitation of the present study is that it was limited to a single center and was retrospective. Even though single-center studies have less methodological variability than collaborative efforts including many centers, only a limited number of subjects can be studied at a single study site. Further genotype-phenotype characterizations in OI will therefore benefit from the continuing expansion of research networks for rare disorders. In conclusion, this study shows that patients with the “mildest” form of OI, caused by COL1A1 haploinsufficiency mutations, have very high rates of significant skeletal involvement. Systematic follow-up of such patients, including radiographic screening for vertebral compression fractures and scoliosis in growing patients, seems warranted.

**Disclosures**

All authors state that they have no conflicts of interest.

**Acknowledgments**

This study was supported by the Shriners of North America. FR received salary support from the Chercheur-Boursier Clinicien program of the Fonds de recherche du Québec en Santé. We thank Liljana Lalic for performing COL1A1 sequence analyses.

Authors’ roles: IMBA and FR: Data design, data collection, data analysis, data interpretation, drafting manuscript, revising manuscript content, approving final version of manuscript, and responsibility for the integrity of the data analysis. PR and FG: Data collection, revising manuscript content, and approving final version of manuscript.

**References**


