Osteoporos Int (2016) 27:3427–3437
DOI 10.1007/s00198-016-3723-3

REVIEW

Osteogenesis imperfecta in children and adolescents—new developments in diagnosis and treatment

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Received: 7 June 2016 / Accepted: 25 July 2016 / Published online: 5 August 2016

Abstract Osteogenesis imperfecta (OI) is the most prevalent heritable bone fragility disorder in children. It has been known for three decades that the majority of individuals with OI have mutations in *COL1A1* or *COL1A2*, the two genes coding for collagen type I alpha chains, but in the past 10 years defects in at least 17 other genes have been linked to OI. Almost all individuals with a typical OI phenotype have a mutation in one of the currently known genes. Regarding medical treatment, intravenous bisphosphonate therapy is the most widely used medical approach. This has a marked effect on vertebra in growing children and can lead to vertebral reshaping after compression fractures, but there is little effect of bisphosphonate therapy on the development of scoliosis. Bisphosphonate treatment decreases long-bone fracture rates, but such fractures are still frequent. Newer medications with antiresorptive and bone anabolic action are being investigated in an attempt to improve on the efficacy of bisphosphonates but the safety and efficacy of these new approaches in children with OI is not yet established.

Keywords Bisphosphonate · Bone fragility · Collagen · Fractures · Osteoblast · Osteogenesis imperfecta

This study was supported by the Shriners of North America and the Fonds de recherche du Québec–Santé

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Introduction

Osteogenesis imperfecta (OI) is a heritable disorder that is mainly characterized by bone fragility, even though many other organ systems can be involved. The typical clinical description of OI also includes blue or gray discoloration of the sclera and tooth abnormalities called dentinogenesis imperfecta [1], but these extraskeletal features of OI are frequently absent.

Even though OI has been recognized as a separate disorder for more than a century, scientific and research interest in this disorder has increased markedly in the past decade. Several recent reviews have provided excellent overviews of the pathophysiology and genetics of OI and related disorders [1–3]. General introductions to OI are also available [4–7]. The present review highlights recent developments in diagnosis and treatment of OI that are of relevance to the clinical metabolic bone disease specialist who is following young patients with OI.

Classification

The severity of bone fragility in OI varies widely. This is reflected in the clinical Sillence classification from 1979 that separated the severity spectrum of OI into four categories (OI types I to IV) [8]. These OI types are still found in the 2015 Nosology and Classification of Genetic Skeletal Disorders [9]. OI type I represents the mildest end of the spectrum with straight limbs ("non-deforming OI"), OI type II usually leads to death shortly after birth ("perinatally lethal OI"), OI type III is the most severe form of the disease in individuals surviving the neonatal period ("progressively deforming OI"), and OI type IV is characterized by a disease severity intermediate between OI types I and III ("moderate severity OI") [9].

Subsequent to the original Sillence classification, additional clinical OI types were delineated, based on distinctive phenotypic characteristics (OI type V, hyperplastic callus formation; OI type VI, accumulation of unmineralized osteoid on bone histology; OI type VII, rhizomelia) [10]. However, the clinical diagnosis of OI type VI is based on the evaluation of bone tissue [11], which often is not available for analysis, and OI type VII has only been observed in an isolated community in Canada [12]. Consequently, five clinical types of OI are generally recognizable with routine diagnostic methods (history, clinical examination, radiographs).

More recently, genotypic OI types (designated as OI type VIII and OI types with higher numbers) have been listed in the widely used Online Mendelian Inheritance of Man (OMIM; http://www.ncbi.nlm.nih.gov/omim/) database, where each discovery of a new OI-associated gene has given rise to a new OI type. However, admixing gene-based OI types to an initially phenotypic classification is controversial [13]. The clinically defined OI types are a convenient short-hand system for describing a spectrum of complex phenotypes with a single number; this facilitates communication. In contrast, converting the name of an OI-related gene into an OI type number makes communication more difficult—it is simpler to just name the involved gene. Here we therefore use the phenotype-based classification proposed by the 2015 Nosology and Classification of Genetic Skeletal Disorders [9] (Table 1).

Genes associated with OI

It has been known for more than three decades that OI phenotypes are most often caused by dominant alterations in one of the genes coding for collagen type I alpha chains *COL1A1* (coding for the collagen type I alpha 1 chain, 1 (I)) or *COL1A2* (coding for 2 (I)) [1]. The molecular diagnosis of OI was initially performed by examining collagen type I protein from skin fibroblasts [14] and later by Sanger sequencing of *COL1A1* and *COL1A2*. In the most detailed Sanger sequencing study to date, pathogenic *COL1A1* or *COL1A2* sequence alterations were detected in 87 % of 142 children with a "typical OI" phenotype [15]. However, the diagnostic yield varied with the phenotypic group. Pathogenic variants were found in 94 % of individuals with OI type I, in 88 % of patients with OI type III but in only 63 % of children with OI type IV.

Starting in 2006, defects in at least 17 genes other than *COL1A1* and *COL1A2* have been linked to OI phenotypes [1] (Table 1). These genes are all expressed in osteoblasts, and the majority of them are directly involved in collagen type I metabolism even though some of these genes seem to play a role in other aspects of osteoblast function [1] (Table 1). Defects in the newer OI-related genes usually lead to recessive forms of OI, but two genes (*IFITM5*, *P4HB*) are associated with dominant OI. Defects in one gene (*PLS3*) lead to X-linked bone fragility.

These new genetic discoveries raise the issue of what genes should be deemed "OI-related genes" and, indeed, what is the definition of OI. In contrast to some other congenital disorders, there are no agreed clinical criteria that define OI. Fractures are the typical hallmark of OI but may result from a variety of other genetic and non-genetic conditions as well [16, 17]. Most authors seem to agree that bone fragility leading to bone deformities should be diagnosed as OI unless there are obvious signs of another genetic disorder [1–3].

In contrast, the "correct" classification of bone fragility without bone deformities is not clear, unless there are "typical extraskeletal features" of OI, such as blue/gray sclera or dentinogenesis imperfecta, leading to a diagnosis of OI type I. However, typical extraskeletal features of OI can be absent even when bone fragility is caused by "typical" OI mutations in *COL1A1* or *COL1A2* [18]. When the constellation of bone fragility, white sclera, and white teeth is caused by mutations in genes other than *COL1A1* or *COL1A2*, such as dominant mutations in *WNT1*, *LRP5*, or *PLS3*, terms such as "idiopathic juvenile osteoporosis," "juvenile osteoporosis," or "early-onset osteoporosis" are used in the literature [2, 3], even though *PLS3* mutations have also been classified among the causes of OI type I [19] and are listed in the OI variant database. This is an area that requires further discussion among stakeholders.

Genotype-phenotype correlations

More than 1500 different mutations have been associated with OI and are listed in the OI variant database (http://www.le.ac.uk/ge/collagen/). Close to 90 % of these mutations affect *COL1A1* or *COL1A2*. Establishing genotype-phenotype correlations is notoriously difficult, but a few principles have emerged.

The most consistent genotype-phenotype correlation is that *COL1A1* mutations leading to 1 (I) haploinsufficiency give rise to OI type I, with mild bone fragility, blue/gray sclera, and normal-looking teeth. The usual causes of 1 (I) haploinsufficiency are *COL1A1* stop or frameshift mutations [20], but splice site mutations and deletions of the entire *COL1A1* gene can have the same clinical outcome [21, 22]. Even though OI type I is also called "mild OI," the bone fragility is still substantial. Compared to the general population, children with *COL1A1* haploinsufficiency mutations have an almost 100-fold increased rate of femur and tibia fractures [23]. The majority of individuals with 1 (I) haploinsufficiency mutations have vertebral compression fractures during childhood or adolescence and about a third develop scoliosis.

Table 1 Genes that have been associated with OI

Gene	Protein	Protein full name	Clinical OI type	Mutations (*N*)	Comment
COL1A1	COL1A1	Collagen type I alpha 1 chain	I, II, III, IV	848	
COL1A2	COL1A2	Collagen type I alpha 2 chain	I, II, III, IV	510	
Collagen type I processing defects					
CRTAP	CRTAP	Cartilage-associated protein	III, IV	24	
P3H1	P3H1	Prolyl-3-hydroxlase 1	III	49	
PPIB	CypB	Cyclophyllin B	III	10	
FKBP10	FKBP65	FK506 binding protein, 65 kDa	III, IV	25	
SERPINH1	HSP47	Heat-shock protein 47	III, IV	2	
PLOD2	LH2	Lysyl hydroxylase 2	III, IV	12	
TMEM38B	TMEM38B	Transmembrane protein 38B	IV	3	
BMP1	BMP1	Bone morphogenetic protein 1	I, III, IV	11	
SEC24D	SEC24D	SEC24D	III, IV	3	
SPARC	SPARC	Secreted protein, acidic, cysteine-rich	IV	2	
P4HB	PDI	Protein disulfide isomerase	III	1	Cole-Carpenter Syndrome
Osteoblast signaling defects					
SP7	SP7	Osterix; transcription factor Sp7	III	1	
WNT1	WNT1	WNT1	IV	18	
Other osteoblast genes, function to be determined					
SERPINF1	PEDF	Pigment-epithelium derived factor	III, IV	21	When bone histology is available: OI type VI
IFITM5	BRIL	Bone-restricted Ifitm-like	V	2	
CREB3L1	OASIS	Old astrocyte specifically induced substance	II	1	
Gene defects with phenotypes similar to OI					
WNT1	WNT1	WNT1		18	Dominant: juvenile osteoporosis
PLS3	Plastin-3	Plastin-3		7	X-linked osteoporosis
LRP5	LRP5	LDL receptor related protein 5		50[#]	Recessive: osteoporosis pseudoglioma syndrome; dominant: juvenile osteoporosis

Mild, straight legs (OI type I); moderate, leg deformity (OI type IV); severe, leg deformity (OI type III); lethal, does not survive neonatal period (OI type II)

[#] Information from the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/). All other data on the number of mutations is from the OI Variant Databse (https://oi.gene.le.ac.uk)

Although OI type I is most often caused by 1 (I) haploinsufficiency mutations, glycine substitutions in the triple helical domain of the 1 (I) or 2 (I) chain can also lead to an OI type I phenotype [15, 18]. In particular, glycine substitutions in the first 125 residues of the 1 (I) or 2 (I) triple-helical domains often are associated with blue or gray sclera and normal-looking teeth (i.e., absence of dentinogenesis imperfecta), similar to 1 (I) haploinsufficiency mutations [15, 18]. However, some mutations affecting the first 90 amino acids are also associated with marked joint hyperlaxity [24]. Glycine substitutions in other parts of the 1 (I) or 2 (I) triple helical domains often lead to OI types II, III, or IV, but the phenotype associated with a given substitution is often hard to predict or to explain [25].

Insights from new sequencing databases raise the possibility that many "typical OI mutations" do not cause an OI phenotype. The ExAc database (version 0.3; http://exac.broadinstitute.org/) contains whole-exome sequencing results from 60,706 unrelated individuals who are not diagnosed with genetic disorders. Of these, 43 have the types of *COL1A1* or *COL1A2* mutations that are generally thought to lead to OI (38 individuals with glycine substitutions in the helical domains of 1 (I) or 2 (I); 5 individuals with *COL1A1* frameshift mutations). Thus, the combined frequency of "typical OI mutations" in the ExAc database (about 70 per 100,000 individuals) is several fold greater than the prevalence of OI (about 10 per 100,000 individuals), suggesting that the majority of individuals who have OI mutations are not diagnosed as having OI.

Mutations in genes other than *COL1A1* and *COL1A2* are usually associated with a moderate to severe phenotype (OI type III, IV, or V). However, there are some exceptions. A recessive *BMP1* mutation affecting the polyadenylation signal of one *BMP1* transcript is associated with a mild disease course that is similar to OI type I [26]. Mutations in *PLS3* also

lead to a mild bone fragility phenotype that can be difficult to distinguish from OI type I [27].

Molecular diagnosis

The diagnosis of OI types, as proposed by the 2015 Nosology and Classification of Genetic Skeletal Disorders, can usually be made using patient history, clinical examination, and radiographs. Molecular diagnosis by DNA sequence analysis is nevertheless useful to pinpoint the exact cause of OI. A typical diagnostic workup is shown in Fig. 1. Molecular diagnosis not only provides precise information about recurrence risk (dominant vs recessive OI) to affected individuals and their families, but also allows identifying affected family members with a high degree of certainty. This is particularly important in OI type I, where clinical signs of the disease can be subtle. However, molecular diagnosis has a very low yield in infants that are evaluated for suspected child abuse and in whom careful clinical examination has not revealed clinical features of OI [17, 28].

Molecular diagnosis can have direct consequences for the clinical management of individual patients. For example, the clinical diagnosis of OI type V is based on the presence of hyperplastic callus or ossification of the interosseous membrane at the forearm, but these features may not be present in young children [29, 30]. Finding the OI type V-specific *IFITM5* mutation alerts the clinician that the patient has a high risk of OI type V complications, such as hyperplastic callus formation [31], radial head dislocation [32], and abnormalities in the cranio-cervical junction [33].

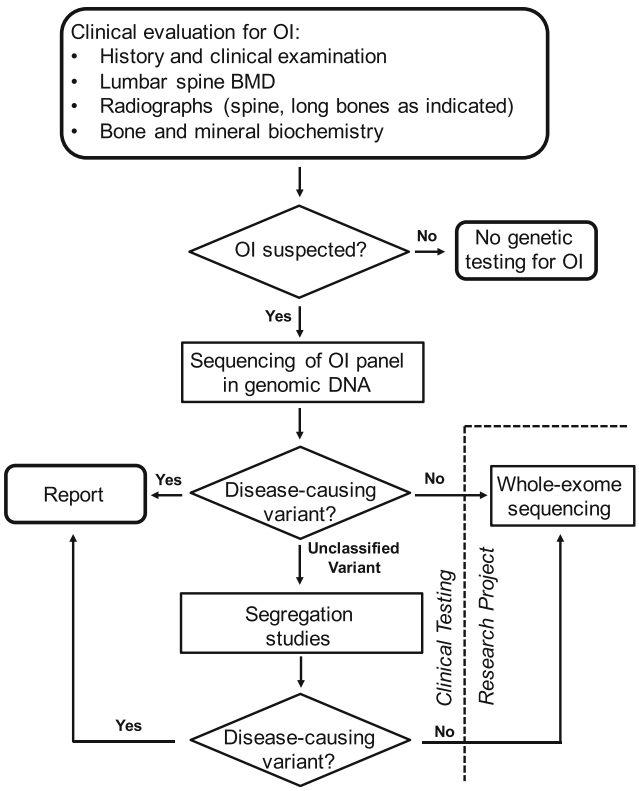

Fig. 1 Diagnostic workup for OI, as used at the authors' institution. When OI is suspected after clinical evaluation, sequence analysis of an OI panel is performed using a next-generation sequencing method, as described [39]

Triple-helical glycine substitutions caused by mutations in exon 49 of *COL1A2* have been found in children with OI who had intracranial hemorrhage and brachydactyly [34]. Mutations affecting the C-propeptide of 1 (I) are frequently associated with hip dysplasia [35]. Identifying bi-allelic *SERPINF1* mutations may influence the choice of medical treatment, as intravenous bisphosphonate therapy is probably less effective in the presence of *SERPINF1* mutations than in OI due to other causes. Treatment with RANKL antibody treatment has shown promising effects in some patients with *SERPINF1* mutations [36, 37].

The molecular diagnosis of OI at present is typically performed by DNA sequence analysis of targeted gene panels ("next-generation sequencing") [38, 39]. The advantage of these methodologies compared to traditional Sanger sequence analysis is that all known OI-related genes can be analyzed in a single analysis run, which reduces analysis time and cost. In the experience of our molecular diagnosis laboratory, gene panel analysis of currently known OI genes identifies disease-causing mutations in at least 97 % of individuals who have a clinical diagnosis of "typical OI" ($n = 598$) [40].

Treatment of OI

The therapeutic goals in OI vary with phenotype and mobility status. Children with uncomplicated OI type I may have similar levels of physical activity as their healthy peers [41]. Therefore, orthopedic and rehabilitation treatments in mild OI are typically limited to fracture management. In this context, medical follow-up chiefly serves to screen for complications, such as vertebral compression fractures, which in many centers would prompt intravenous bisphosphonate treatment [42–44]. In contrast, moderate to severe OI is often associated with long-bone deformities, scoliosis, and reduced mobility, creating the need for orthopedic and rehabilitation interventions. Such interventions are essential for adequate care of patients with moderate to severe OI but are beyond the scope of the present contribution.

Ensuring that vitamin D serum levels remain "sufficient" is a frequently cited goal in the supportive medical management of OI [5, 45, 46], but the evidence base for any specific 25-hydroxyvitamin D target level is thin. A bone histomorphometric study on 71 children with OI found no evidence that 25-hydroxyvitamin D levels in the range from 13 to 103 nmol/L were associated with measures of bone mineralization, metabolism, or mass [47]. However, two

cross-sectional retrospective studies observed a relationship between vitamin D status and bone mineral density (BMD) [48, 49]. Higher-level evidence was provided by a recent randomized controlled trial on 60 children with OI that compared two doses of vitamin D supplementation: 400 and 2000 international units [50]. The group receiving 2000 international units of vitamin D had higher 25-hydroxyvitamin D serum levels, but no differences in lumbar spine areal BMD or any other outcome measures were detected. However, in the 12 patients with baseline 25-hydroxyvitamin D serum levels below 50 nmol/L, lumbar spine areal BMD tended to increase faster in the group receiving 2000 international units of vitamin D. It is thus possible that this higher dose of vitamin D is beneficial to patients with 25-hydroxyvitamin D serum levels below 50 nmol/L, but further studies that specifically target this group of patients are needed for verification.

Bisphosphonate treatment

Bisphosphonate therapy has been given to children with OI for three decades [51] and this is by far the most widely used medical treatment modality, even though many different protocols have been proposed. The bisphosphonate treatment approach used by the authors is shown in Fig. 2. Hundreds of publications have reported on bisphosphonate treatment in OI and concur that it leads to an increase in areal BMD at the spine and several other skeletal sites [52–54]. This is not surprising, given that bone formation activity is very high during growth, and even more elevated in severe OI, and is not coupled to bone resorption in skeletal locations undergoing bone modeling [55, 56]. Anti-osteoclast treatment will therefore reliably increase bone mass as long as skeletal growth continues.

More controversial is the question of what clinically relevant benefit children with OI derive from higher areal BMD. Treatment outcomes such as fracture rate, mobility, and quality of life are difficult to assess in OI due to the rarity and heterogeneity of the disorder, the developmental changes occurring during childhood, the multifactorial origin of fractures, and the variability of concurrent orthopedic and rehabilitation treatments. Large long-term studies would be needed to account for these confounding variables.

Recent systematic reviews have summarized the evidence from randomized trials on bisphosphonates in OI [52–54]. These systematic reviews agree that the available evidence is insufficient to judge whether bisphosphonate therapy improves outcomes other than areal BMD and that more studies are needed. This conclusion reflects the fact that available trials were underpowered to assess outcomes other than areal BMD and had short treatment durations. However, the reality is that large placebo-controlled long-term trials on bisphosphonates in OI are unlikely to be conducted. Obstacles to such trials include lack of funding, the difficulty

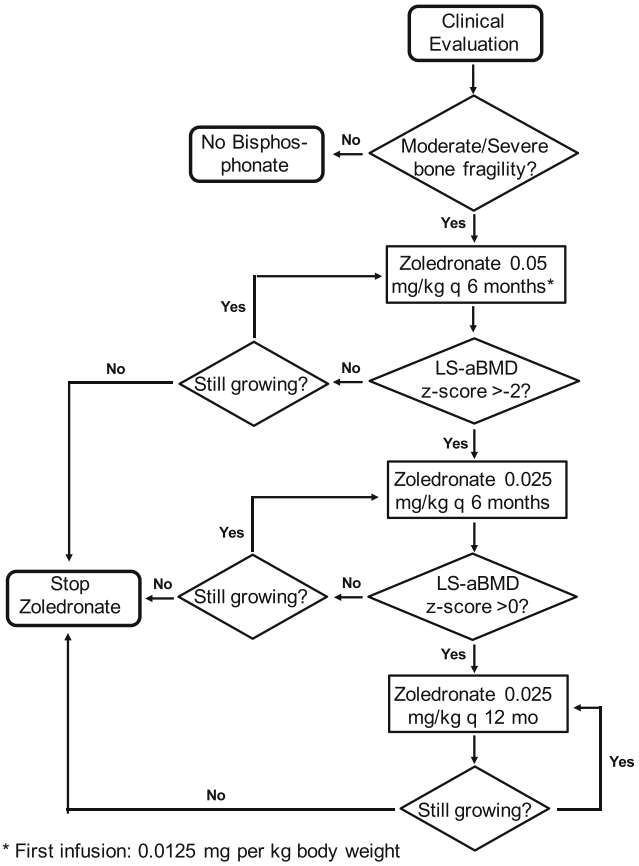

Fig. 2 Bisphosphonate treatment approach as used by the authors to treat children with OI who are 2 years of age or older. Intravenous zoledronate is administered at a dose that depends on lumbar spine areal BMD (LS-aBMD) results. With this approach, children with less severe forms of OI will receive a lower total exposure of zoledronate than children with more severe forms of OI. The reason for this is that children with less severe OI reach the indicated LS-aBMD cutoffs more quickly. Note that the first exposure to intravenous zoledronate occurs at a lower dose to minimize adverse events (in particular hypocalcemia and the "acute phase reaction") [75]. Once patients have reached final height, the treatment is discontinued [107]. Long-term results of this approach have been described [61]

of finding patients who are willing to risk being randomized to placebo, and the lack of equipoise about treatment benefits among clinicians who have experience with bisphosphonate treatment in OI. Most likely therefore, clinicians will continue to make treatment recommendations that are informed by less-than-ideal evidence.

Effect of bisphosphonates on the spine

Intravenous bisphosphonate therapy has a marked effect on the spine of growing children with OI. When vertebral compression fractures are present at the start of therapy, these tend to reshape, i.e., vertebra gain a more normal shape through growth (Fig. 3) [44, 57–60]. As reshaping of compressed vertebra is a growth-dependent process, the potential for correcting the shape of compressed vertebra depends on how

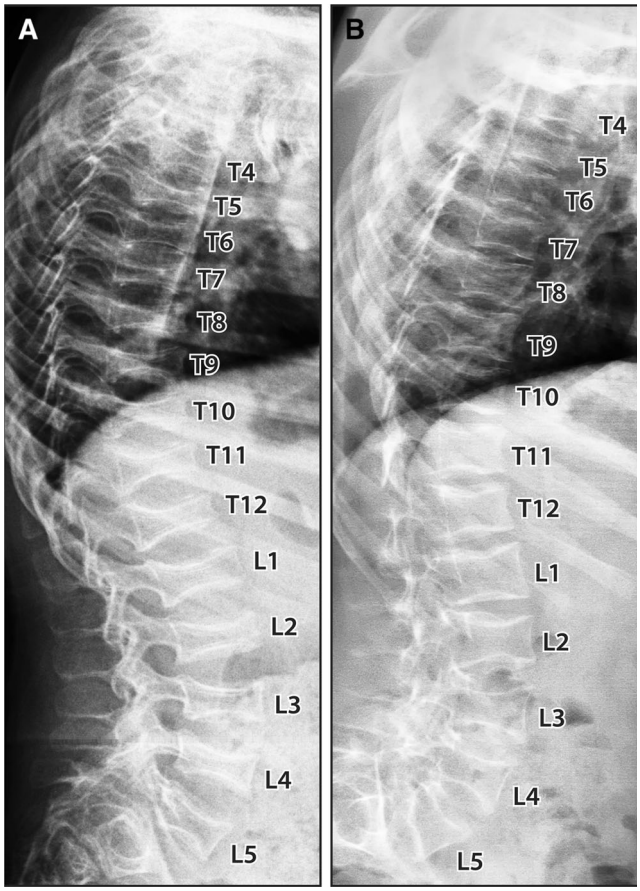

Fig. 3 Reshaping of vertebral bodies in a boy with OI type IV at 12.0 years of age (**a**) and after 4 years of treatment with intravenous zoledronate (**b**)

much growth remains at the time of treatment inception. A recent study in children with moderate to severe OI who started intravenous bisphosphonate therapy before 5 years of age found that the majority of compressed vertebra had regained a normal shape by the time the children had finished growing [61].

It is not clear that the positive spine effects of intravenous bisphosphonate treatment are also achieved by oral bisphosphonates. The largest trial on OI conducted to date ($n = 147$ participants) did not find an effect of oral risedronate on vertebral fractures [62]. A similarly sized randomized placebo-controlled trial on oral alendronate ($n = 139$) also did not observe improvements in vertebral shape [63]. However, it is possible that the observation intervals in these studies on oral bisphosphonates were too short to detect vertebral effects.

Intravenous bisphosphonate therapy, despite improvements in the shape of individual vertebra, does not seem to have a major effect on the development of scoliosis (Fig. 4). Two recent studies who in aggregate examined about 750 individuals with OI concordantly concluded that intravenous bisphosphonate treatment somewhat decreased the 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 [64, 65]. More importantly, the prevalence of scoliosis at maturity was not influenced by bisphosphonate treatment history in any OI type. It thus appears that bisphosphonate therapy may slow the progression of scoliosis in the most severely affected patients but does not change the final outcome.

Effects of bisphosphonates on long bones

Both oral and intravenous bisphosphonate therapy seem to be associated with a lower rate of long-bone fractures in children with OI ([43, 61, 62, 66, 67]). Reported fracture rate reductions are typically in the range of 30 to 60 %, which indicates some therapeutic efficacy but also implies that a large number of long-bone fractures continue to occur. Indeed, a recent

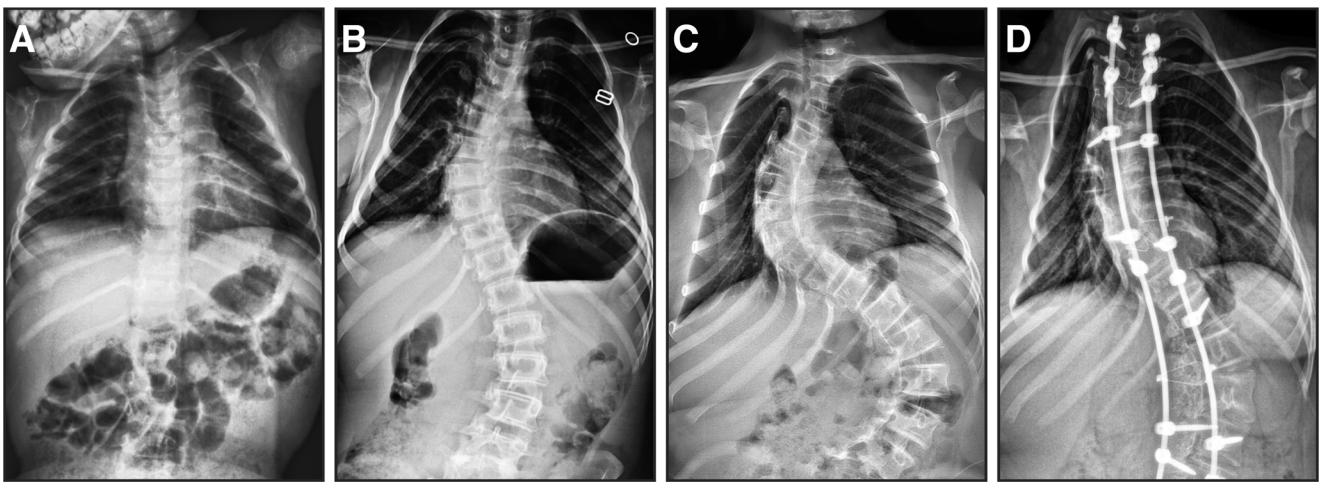

Fig. 4 Progression of spine curvature in a girl with OI type IV at the age of 3.4 years (**a**), 11.9 years (**b**), 13.6 years (**c**), and 15.0 years (**d**). Treatment with intravenous bisphosphonates was started at 3.4 years of age and continued until 15.4 years of age (initially pamidronate; zoledronate after the age of 10.3 years). Spinal fusion surgery was performed at the age of 14.4 years

study followed a group of 37 children with moderate to severe OI for 15 years after the start of intravenous bisphosphonate therapy and documented a median of 6 femur and 5 tibia fractures per patient [61]. Thus, long-bone fractures are clearly still a major problem despite bisphosphonate treatment.

Several factors may contribute to this persistence of high long-bone fracture rates during bisphosphonate treatment. Children with OI have long-bone diaphyses with a very small bone cross - section, indicating decreased periosteal bone growth [68]. Total volumetric BMD of long-bone diaphyses is therefore abnormally high in OI, which is in marked contrast to the low BMD at metaphyseal sites [69]. Bisphosphonate treatment has no obvious effect on the cross-sectional size of long-bone shafts [61] and may have limited scope for increasing BMD when total volumetric BMD is already elevated. Material bone properties are also decreased in long-bone diaphyses of children with OI [70], and material properties of OI bone are not detectably altered by bisphosphonate therapy [71]. Another factor contributing to long-bone fractures in many children with moderate to severe OI are bone deformities. These do not respond to any known medical intervention but rather need to be corrected by surgical intervention.

Despite the continued occurrence of long-bone fractures, it has long been noted that intravenous bisphosphonate treatment can improve mobility, especially when started in the first few years of life [44, 59]. Long-term follow-up suggests that most children with OI type IV, but not those with OI type III, achieve the ability to walk independently [72]. In individuals with OI type III, the functional goal typically is to achieve the ability to live independently despite restricted mobility [72].

Potential adverse events of bisphosphonates

Hypocalcemia, fever, and vomiting are well-known adverse events during the first exposure to intravenous bisphosphonates such as pamidronate, ibandronate, or zoledronate [73–77]. An apparently life-threatening systemic response to the first dose of zoledronic acid has been reported in one child (with a diagnosis other than OI) [78]. Acute deterioration of respiratory status has also been reported in infants and young children with OI who were receiving pamidronate [79, 80]. It is an important responsibility of physicians administering bisphosphonates to report such severe adverse events to drug safety systems such as MedWatch of the Food and Drug Administration (http://www.fda.gov/Safety/MedWatch/).

Among the longer-term potential adverse events of bisphosphonates, osteonecrosis of the jaw is a frequently mentioned concern that has undergone intense scrutiny. However, a recent systematic review did not identify any confirmed occurrence in children with OI [81] and there seem to be no reported cases in adults with OI either. Some experts have nevertheless recommended performing a dental review on all children starting bisphosphonate treatment and to complete any necessary dental work prior to the first bisphosphonate infusion [82].

As many children with moderate to severe OI undergo intramedullary rodding surgery to correct bone deformities, the interplay between bisphosphonate therapy and osteotomy healing is a clinically important topic. It had previously been found that intravenous pamidronate therapy was associated with an increased rate in delayed healing of osteotomy sites, but not of fracture sites [83]. A follow-up study was performed after changes in surgical technique as well in bisphosphonate infusion protocol (infusions were no longer given in the 4 months following the osteotomy) had been implemented. A review of 261 rodding procedures on 110 patients showed that delayed osteotomy healing still occurred but that the incidence was markedly reduced under the modified approach [84].

A number of recent case reports have suggested that atypical femur fractures occur in children and adults with OI who had received bisphosphonate therapy [85–89]. The diagnostic entity of atypical femur fractures was originally established to describe a specific type of diaphyseal femur fractures in women with postmenopausal osteoporosis who had received anti-resorptive treatment [90]. However, fracture epidemiology is not as well characterized in OI as it is in postmenopausal osteoporosis. It is therefore not clear that the type of femur fracture that would be deemed atypical in the context of postmenopausal osteoporosis is actually atypical for individuals with OI. Indeed, transverse diaphyseal femur fractures (the key feature of atypical femur fractures [90]) have been among the most common fractures in OI even before the bisphosphonate era [91]. Systematic studies are necessary to assess whether the prevalence of "atypical femur fractures" is higher in bisphosphonate-treated individuals.

Drugs other than bisphosphonates

Even though most children with moderate to severe OI benefit from bisphosphonate therapy, it is obvious that there is a lot of room for further improvement. Alternative medical approaches are therefore being investigated.

The options for anti-resorptive therapy are not limited to bisphosphonates. Osteoclast inhibition can also be achieved with denosumab, a drug based on an antibody against RANKL. Denosumab is approved for the treatment of postmenopausal osteoporosis and other skeletal disorders in adults. A few case series have been published on the use of denosumab in children with OI caused by *SERPINF1* mutations [36, 37] and in patients with *COL1A1* or *COL1A2* mutations [92]. In both situations, a decrease in bone metabolism markers and an increase in areal BMD were observed.

On a bone histological level, denosumab seems to have a similar effect on growing children as intravenous pamidronate [93, 94]. However, denosumab has a much shorter duration of

action than bisphosphonates, which can be seen as an advantage because it allows better control of the duration of anti-resorptive action. The reverse side of the shorter duration of osteoclast inhibition is that potentially severe "rebound hypercalcemia" may occur when the anti-resorptive activity of denosumab ceases [95, 96]. This has not been observed in the reported children with OI who received denosumab, but these children had all previously been treated with bisphosphonates, which presumably prevents a sudden surge in osteoclast activity after denosumab treatment.

As the genetic defect underlying OI primarily affects the osteoblast, it is intuitively appealing to attempt therapy with stimulators of bone formation. A randomized controlled trial on teriparatide in adults with OI showed increased BMD in mild OI and less effect in moderate to severe OI [97]. Another approach to stimulate bone formation is through antibody-mediated sclerostin inhibition. Sclerostin antibody treatment has shown promise in several OI mouse models with mild bone involvement [98–100]. However, the beneficial effect of sclerostin inhibition was less obvious in a mouse model of more severe dominant OI [101]. Clinical experience with sclerostin antibody treatment of OI has not yet been reported.

One potential issue with bone anabolic agents in OI is that bone formation rate is markedly increased in children with moderate to severe OI prior to any bone-specific treatment [55, 102]. Somewhat counterintuitively, the low bone mass in OI is therefore not caused by a lack of bone formation activity but by high bone resorption. This may limit the effectiveness of bone anabolic treatments unless bone resorption is inhibited at the same time. A combination therapy using both an anabolic and an anti-resorptive agent therefore appears intuitively appealing, similar to the situation in postmenopausal osteoporosis, where this approach has shown promising results [103].

Outlook

The study of rare diseases often requires collection of data from large catchment areas and collaboration between centers. In OI, several such collaboration are under way using registries [104, 105], research networks supported by patient advocacy organizations [106], or industry-sponsored pharmaceutical trials. Novel developments include the establishment of the Brittle Bone Disease Consortium (https://www.rarediseasesnetwork.org/cms/BBD) that is supported by the National Institutes of Health in the USA and similar efforts in Europe. These collaborative efforts will help to accelerate the development of novel therapeutic approaches and their application to clinical practice.

Acknowledgments F.R. received salary support from the Chercheur-Boursier Clinicien program of the Fonds de Recherche du Québec–Santé and was supported by the Shriners of North America.

Conflicts of interest Pamela Trejo and Frank Rauch declare that they have no conflict of interest.

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