Update on the Evaluation and Treatment of Osteogenesis Imperfecta

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Osteogenesis imperfecta (OI) is a term used to describe a group of inherited connective tissue conditions that are characterized by increased bone fragility and low bone mass. With an estimated prevalence of 1 in 12,000 to 15,000 children,\textsuperscript{1,2} it has a broad clinical phenotype, ranging in severity from perinatal lethality to mild clinical forms without fractures. Wormian bones are present in the skull in approximately 60% of patients (Fig. 1).\textsuperscript{3} Other clinical characteristics such as blue sclera, dental abnormalities, skin hyperlaxity, and joint hypermobility are heterogeneous in presentation even in affected members of the same family.

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KEYWORDS

- Osteogenesis imperfecta
- Collagen
- Fractures
- Bisphosphonates

KEY POINTS

- Osteogenesis imperfecta (OI) is the most common cause of primary osteoporosis in children and presents with variable severity.  
- Ninety percent of cases of OI are due to autosomal dominant mutations of type 1 collagen genes, but new genes involved with post-translational collagen modification have been recently implicated in rare recessive forms.  
- Fracture management emphasizes minimizing time and extent of immobilization to minimize secondary disuse osteoporosis. Surgical management of long bone fractures and deformities includes intramedullary fixation devices.  
- Bisphosphonate therapy can increase bone mineral density and decrease bone pain and fracture incidence. The optimal treatment regimen and duration is unknown.
Most of the cases are associated with mutations in 1 of 2 genes that encode the alpha chains of collagen type I (COL1A1 and COL1A2). Over the past 10 years, multiple additional genes involved with post-translational modification of type 1 collagen, bone cell signaling, or regulation of bone matrix homeostasis have been identified, expanding the genetic spectrum of OI.

**CLASSIFICATION OF OSTEOGENESIS IMPERFECTA**

The Sillence classification, published in 1979, was the first systemic classification of OI phenotype, divided based on clinical and radiographic criteria. Patients were classified as having mild nondeforming (type I), moderate (type IV), severe progressively deforming (type III), or perinatal lethal (type II) OI. With increased awareness of the genetic complexity of OI and the phenotypic variability arising from mutations at single loci, there is ongoing debate about the optimal method to categorize patients. Tables 1 and 2 outline the current known genetic mutations associated with OI. Careful analysis of the inheritance pattern and clinical phenotype can help guide genetic testing.

**Autosomal Dominant Osteogenesis Imperfecta**

Autosomal dominant mutations in COL1A1 or COL1A2 account for approximately 90% cases of OI (see Table 1). Type I OI arises from a quantitative defect in collagen production due to a silenced allele of the COL1A1 gene. Usually as a result of a premature stop codon within the gene, these mutations lead to half of the normal amount of protein production. The structure of the type 1 collagen protein that is produced is normal. Type 1 OI presents with fractures, typically before puberty, and is nondeforming. With the completion of growth the incidence of fractures decreases.

In comparison, type II, III, and IV OI are a result of structural defects in type I collagen due to missense mutations in either the COL1A1 or COL1A2 gene. The most common mutations, involving substitution of glycine by a larger amino acid, disrupt the triple helix assembly of collagen, impairing its function and interactions with the extracellular matrix. Depending on the helical location of a mutation and the resultant instability of the protein, the clinical phenotype can range from lethal to mildly deforming.
### Table 1
**Autosomal dominant mutations involved in osteogenesis imperfecta**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Disease Mechanism</th>
<th>Skeletal Phenotype</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL1A1</td>
<td>OI type I</td>
<td>Decreased type 1 collagen production</td>
<td>Mild</td>
<td>Nondeforming, most fractures prepubertal, presenile deafness, aortic regurgitation</td>
</tr>
<tr>
<td>COL1A2</td>
<td>OI type II</td>
<td>Abnormal type 1 collagen production</td>
<td>Lethal</td>
<td>Multiple rib, long bone and vertebral fractures, pulmonary hypoplasia, central nervous system malformations and hemorrhages</td>
</tr>
<tr>
<td></td>
<td>OI type III</td>
<td>Abnormal type 1 collagen production</td>
<td>Severe</td>
<td>Triangular facies, short stature, severe long bone deformaties, elongated vertebral pedicles, “popcorn” appearance of metaphyses and epiphyses, decreased ability to ambulate</td>
</tr>
<tr>
<td></td>
<td>OI type IV</td>
<td>Abnormal type 1 collagen production</td>
<td>Moderate</td>
<td>Short stature, may have long bone bowing, scoliosis, and joint laxity</td>
</tr>
<tr>
<td>IFITM5</td>
<td>OI type V</td>
<td>Dysregulation of collagen mineralization</td>
<td>Moderate</td>
<td>Calcification of forearm intraosseous membrane, radial head dislocation, hyperplastic callous formation</td>
</tr>
</tbody>
</table>

### Table 2
**Autosomal recessive mutations involved in osteogenesis imperfecta**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Disease Mechanism</th>
<th>Skeletal Phenotype</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERPINF1</td>
<td>OI type VI</td>
<td>Mineralization defect</td>
<td>Moderate to severe</td>
<td>Healthy at birth with subsequent progressively severe deformities. Undermineralization and “fish-scale” pattern on iliac crest biopsies</td>
</tr>
<tr>
<td>CRTAP</td>
<td>OI type VII</td>
<td>Collagen 3-hydroxylation defect</td>
<td>Severe to lethal</td>
<td>Rhizomelia, neonatal fractures, popcorn metaphyses, short stature</td>
</tr>
<tr>
<td>LEPRE1</td>
<td>OI type VIII</td>
<td>Collagen 3-hydroxylation defect</td>
<td>Severe to lethal</td>
<td>Rhizomelia, popcorn metaphyses, short stature</td>
</tr>
<tr>
<td>PPIB</td>
<td>OI type IX</td>
<td>Collagen 3-hydroxylation defect</td>
<td>Severe</td>
<td>Short stature</td>
</tr>
<tr>
<td>SERPINH1</td>
<td>OI type X</td>
<td>Chaperone defect</td>
<td>Severe</td>
<td>Renal stones</td>
</tr>
<tr>
<td>FKBP10</td>
<td>OI type XI</td>
<td>Chaperone defect</td>
<td>Moderate to severe</td>
<td>Contractures</td>
</tr>
<tr>
<td>BMP1</td>
<td>OI type XII</td>
<td>Defective collagen processing</td>
<td>Severe</td>
<td>Hyperextensibility</td>
</tr>
<tr>
<td>SP7</td>
<td>Unclassified</td>
<td>Impaired osteoblast differentiation</td>
<td>Moderate</td>
<td>Delayed tooth eruption</td>
</tr>
<tr>
<td>WNT1</td>
<td>Unclassified</td>
<td>Impaired osteoblast function</td>
<td>Moderate to severe</td>
<td>Central nervous system malformations</td>
</tr>
</tbody>
</table>
Type II OI is the most severe form of OI and newborns do not generally survive past the perinatal period. Infants present with multiple intrauterine fractures and severe long bone deformities. Pulmonary hypoplasia with multiple rib fractures or central nervous malformations usually result in death. Type III OI is the most severe, nonlethal form and is characterized by history of multiple fractures from infancy, severe long bone deformities, and significant short stature. Children have typical triangular facies from a relatively large skull with underdeveloped facial bones. Multiple vertebral compression fractures cause severe scoliosis, kyphosis, and rib cage deformity. Distortion of the growth plates with partial calcification of cartilage can lead to a popcorn appearance of epiphyses. Ambulation is often limited either to a wheelchair or with aids. Type IV OI, although not as severe as type III, can present with some long limb bowing, vertebral fractures, and relative short stature. Most children are ambulatory, although may need walking aids.

Individuals with type V OI exhibit specific clinical features including calcification of the forearm intraosseous membrane, radiodense metaphyseal bands at growth plates of long bones, and development of hyperplastic callus after trauma. There is an 85% incidence of radial head dislocation. Genetic mutations in the gene encoding interferon-induced transmembrane protein 5 (IFITM5) were discovered in 2012 to be the causative defect. Although IFITM5 appears to play a role in bone ossification, the mechanism by which it regulates collagen mineralization is not known.

**Autosomal Recessive Osteogenesis Imperfecta**

The autosomal recessive forms of OI are rare conditions and account for approximately 2% to 5% of cases. Mutations have been discovered in critical elements involved in type I collagen secretion and post-translation modification (collagen 3-hydroxylation and chaperone defects) as well as signaling and transcription factors involved in osteoblast function (see Table 2). Although the autosomal recessive forms are uncommon, the discovery of multiple new genes responsible for OI has shed light onto new mechanistic pathways and possible therapeutic approaches.

**EXTRASKELETAL CLINICAL FEATURES OF OSTEOGENESIS IMPERFECTA**

**Hearing Loss**

The hearing loss, a mixture of conductive and sensorineural deficiency, is generally progressive, with 50% of adults with OI having hearing loss by 50 years of age (Box 1). The prevalence of hearing difficulties in children with OI is around 5%. The hearing loss is generally progressive, with 50% of adults with OI having hearing loss by 50 years of age (Box 1).

**Dental Abnormalities**

Dentinogenesis imperfecta is characterized by abnormal dentin leading to the appearance of small deformed teeth, which are opalescent due to a higher ratio of transparent enamel to opaque dentin. Primary dentition is more affected than the permanent dentition. The prevalence of dentinogenesis imperfecta in patients with OI is approximately 28%. Malocclusion and delayed tooth eruption can occur in up to 60% to 80% of patients.

**Ocular Changes**

Patients with OI frequently have blue sclera, particularly in type I OI. The scleral color can vary and is generally darker in infancy.
Connective Tissue Features
Joint hyperlaxity is common and can lead to dislocation of joints and the head of the radius. Abnormalities in type I collagen can also result in increased capillary fragility and bruising, decreased elasticity of skin, and hernias.

Hypercalciuria
Hypercalciuria can occur in up to 36% of patients and there is an increased risk for renal calculi.

Cardiovascular Features
In adults with OI, aortic root dilation followed by mitral valve prolapse is the most frequent valvular manifestation.

Neurologic Features
Macrocephaly and hydrocephalus are associated with OI. Basilar invagination (an infolding of the skull case that leads to brainstem distortion) is a rare but potentially fatal complication of OI. Symptoms of basilar invagination include headache, lower cranial nerve palsies, dysphagia, quadriplegia, ataxia, and nystagmus. Early intervention with occipitocervical bracing can delay progression. Cervical spine kyphosis may also rarely cause compression of the cervical spinal cord. Symptoms can include sensory or motor disturbances of the upper or lower extremities progressing to quadriplegia.

DIAGNOSIS AND DIFFERENTIAL
A diagnosis of OI is based on typical clinical and radiological findings. Radiographic features include generalized osteopenia, gracile long bones with evidence of bowing (Fig. 2). Vertebral fractures are common, with a 71% reported prevalence rate in type 1 OI. Spiral and transverse fractures of long bones are seen most commonly in the
lower limbs, and avulsion type fractures, such as olecranon and patellar fractures, occur due to decreased tensile strength of the bone (Fig. 3). Bone mineral density as measured by dual energy radiographic absorptiometry is usually low, but is not specific or diagnostic of OI. Genetic testing can help confirm the diagnosis; however, given that more than 1500 dominant mutations in COL1A1 or COL1A2 have been identified to date, genetic sequencing of either peripheral blood or cultured fibroblasts is required. When feasible, a bone biopsy with histomorphometric analysis may provide additional diagnostic information.

In infants, nonaccidental injury (NAI) is an important diagnosis to differentiate from OI. Although the pattern of fractures (such as posterior rib and metaphyseal fractures) and associated clinical signs of injury (retinal hemorrhage, bruises) may be contributory, differentiating NAI from OI can be difficult. Although typically associated with NAI, rib fractures can be seen in up to 22% of children with OI.

Fig. 2. (A) A lateral view of the femur shows thin cortices, coarse trabeculation, and deformity from a malunited fracture at the distal metadiaphyseal junction. (B) The same femur following osteotomy and placement of a growing intramedullary rod. Notice transverse radiodense growth lines parallel to the femoral and tibial growth plates, indicative of cyclical bisphosphonate infusion.

Fig. 3. (A) An avulsion fracture of the olecranon. The mechanism of injury is tensile failure of bone. Half of children with olecranon fractures have osteogenesis imperfecta. (B) Postoperative radiograph showing repair of the olecranon fracture with a tension band wiring technique.
In older children, idiopathic juvenile osteoporosis (IJO) can also present with a history of frequent fractures. Characteristically typified by bone pain and vertebral fractures before the onset of puberty, the underlying cause has yet to be identified. Transiliac histomorphometry studies in patients with IJO demonstrate decreased trabecular bone volume, number, and thickness. Secondary causes of osteoporosis such as malabsorption, glucocorticoid-induced osteoporosis, hormone deficiencies, acute lymphoblastic leukemia, and immobility should be able to be differentiated based on history and laboratory investigations. Other skeletal disorders resembling OI may also need to be considered in the differential (Table 3).

**MANAGEMENT**

The goals of treatment of OI are to maximize mobility and daily life competencies and decrease bone pain and bone fragility. Management should be multidisciplinary and includes rehabilitation, surgical, and pharmacologic treatment. The degree of intervention needed depends on the severity of the clinical phenotype.

**Rehabilitation**

Physical therapy is used to guide motor skills acquisition for severely involved children and is important in maximizing weight-bearing exercise to prevent fractures or during

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Skeletal conditions resembling osteogenesis imperfecta</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td><strong>Genes</strong></td>
</tr>
<tr>
<td>Osteoporosis pseudoglioma syndrome</td>
<td>LRP5</td>
</tr>
<tr>
<td>Bruck syndrome</td>
<td>PLOD2</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>COL5A1, COL5A2, TNXb, COL3A1</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>ALPL</td>
</tr>
<tr>
<td>Idiopathic hyperphosphatasia</td>
<td>TNFRSSF1IB</td>
</tr>
<tr>
<td>Idiopathic juvenile osteoporosis</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Abbreviations: AD, autosomal dominant; AR, autosomal recessive.*
recovery from fractures. The heterogeneity of the patient population requires a multi-disciplinary approach to setting goals and monitoring progress. Hydrotherapy is a useful means of gradual return to weight-bearing. Wheelchairs and walking aids are prescribed according to the child’s needs, with an ongoing negotiation of the balance between seated mobility for its practical use and weight-bearing exercise to maintain bone strength and ability to assist with transfers. Patients with upper extremity deformities may benefit from occupational therapy assessment to help with self-care and daily living activities.

**Surgical Treatment**

Fractures are the most common reason for a child with OI to see a surgeon. Fracture healing times for children with OI are normal even with bisphosphonate treatment. Excessive immobilization is to be avoided during fracture treatment because it leads to weak, stiff muscles and secondary disuse osteopenia of the bones, which in turn can lead to more fractures.

Fractures in infants are best treated with the simplest form of immobilization with the aim of providing comfort to the limb while the initial fracture callus forms. Fractures heal quickly in infants (2–3 weeks). Once the limb is comfortable and stable an early return to function with guidance from a physical therapist is appropriate.

Toddlers and older children vary considerably in the number of fractures they experience and in the amount of limb deformity that occurs. Limb deformity is a combination of that resulting from healed fractures, as well as additional gradual distortion of the shape of the bone. Some children with OI have little deformity and have fracture patterns similar to those seen in the normal child population. These types of fractures are treated with closed or open management using standard techniques. Plate fixation should be avoided if possible because there is a higher risk of subsequent peri-implant fracture. There is an increased incidence of purely tensile failure of bone—for example transverse fractures of the olecranon or patella—in children with OI. These respond well to tension band wiring and early motion.

Deformities of the femurs and tibiae can be treated with osteotomy and intramedullary rodding either at the time of a fracture or electively. Intramedullary rodding maintains a straight mechanical alignment and supports the whole bone, producing the best biomechanical circumstance for further strengthening with subsequent weight bearing. Modern intramedullary rods are designed to elongate as the child grows. Such growing rods have the advantage of ongoing support and a reduced number of revision operations.

Scoliosis and kyphosis of the thoracolumbar spine are common in children with severe OI. Bracing is controversial particularly in younger children, because there is no evidence that it prevents the progression of scoliosis and because there are concerns about limiting chest wall growth and contributing to restrictive lung disease. Scoliosis is not painful and does not usually interfere with sitting balance or activities of daily living. Spinal fusion with instrumentation has been reported in selected cases but has a high complication rate and is not universally recommended.

Spondylolysis and spondylolisthesis of the lumbosacral spine are observed radiographically in patients with OI but are reported to occur no more frequently than in the general population. This condition is usually minimally symptomatic or asymptomatic and is most often successfully managed nonoperatively.

Cervical spine abnormalities can include kyphosis or spondylolysis and spondylolisthesis. Rarely a progressive and severe cervical spine deformity will threaten...
or compromise cervical cord function. In these cases, careful consideration of operative decompression and fusion, with attendant high complication rates, is warranted.42,43

**Pharmacologic Treatment**

Children with OI should be assessed to ensure that there is sufficient dietary calcium and 25-hydroxyvitamin D intake. One in four children with OI has evidence of vitamin D deficiency, and serum 25-hydroxyvitamin D concentrations are independently associated with bone mineral density.44 The decision to start pharmacotherapy, such as bisphosphonates, depends on the clinical severity of the child (presence of long bone deformities, bone pain, frequent fractures) rather than the bone mineral density or collagen mutation status.

**Bisphosphonates**

Bisphosphonates are analogues of pyrophosphate that bind avidly to the hydroxyapatite crystals in mineralized bone. They decrease osteoclast function and number and thereby inhibit bone resorption.45 Transiliac histomorphometry studies have shown that intravenous bisphosphonates decrease bone resorption on endocortical surfaces while not significantly affecting osteoblast activity on periosteal surfaces, leading to increased cortical bone thickness.46 They are the most widely used pharmacologic treatment in children with OI.

Both controlled and observational trials have demonstrated bisphosphonates significantly increase bone mineral density, with the most gain achieved within the first 2 to 4 years.34 Although observational trials have documented reductions in long bone fracture rate and bone pain, as well as improved vertebral morphology, strength, and activities of daily living,47–49 these results have not always been supported with results from randomized control trials. A summary of randomized controlled trial results of bisphosphonate use in children with OI is outlined in Table 4.50–57

There remain uncertainties about the optimal bisphosphonate dosing schedule and duration. Oral dosing has the advantage of convenience for patients and families but there has been concern about its effectiveness in children with more significant disease. Stopping bisphosphonate treatment while growth remains can result in a reduction in metaphyseal bone mineral content,58 an increased risk for fracture at the junction of the untreated and treated bone.58 However, given the decade-plus half-life of bisphosphonates in bone and concerns of the effect of continuous use on bone matrix quality59 and potential risk for atypical fractures,60 many clinicians have advocated for intermittent treatment. To date, there have not been any randomized controlled trials to address the optimal treatment duration.

Bisphosphonate treatment is associated with flulike symptoms in up to 85% of children following the first dose and can lead to transient hypocalcemia.61 Decreased bone remodeling associated with treatment can delay the healing of osteotomy sites following intramedullary rodding.52 Osteonecrosis of the jaw has been described in adult patients on bisphosphonate therapy63 but has not reported in pediatric patients with OI to date.

**Growth hormone**

Growth hormone has been trialed given its potential anabolic effects on bone through stimulation of osteoblasts, collagen synthesis, and bone growth.64 Growth hormone deficiency is uncommon in children with OI.65 Growth hormone treatment can however increase growth velocity in children with OI,66,67 although there are no data on its effect on final adult height. Growth hormone has been shown to increase
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Peripheral Fracture Rate</th>
<th>Vertebral Fracture Rate</th>
<th>Lumbar Spine BMD</th>
<th>Bone Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral bisphosphonate randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sakkers et al, 50 2004</td>
<td>Olpadronate vs placebo for 2 y</td>
<td>n = 34</td>
<td>31% decrease</td>
<td>No difference</td>
<td>Increased (gain of 1.67 SD vs 0.14 SD)</td>
<td>n/a</td>
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<tr>
<td></td>
<td></td>
<td>10.4 ± 3.5 y (range 3–18)</td>
<td></td>
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<td></td>
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<tr>
<td>Seikaly et al, 51 2005</td>
<td>Alendronate vs placebo for 1 y</td>
<td>n = 20</td>
<td>No difference</td>
<td>No difference</td>
<td>Increased (gain of 0.89 SD vs loss of 0.12 SD)</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.8 ± 1.1 y (range 3–15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward et al, 52 2011</td>
<td>Alendronate vs placebo for 2 y</td>
<td>n = 139</td>
<td>No difference</td>
<td>No difference</td>
<td>Increased (gain of 1.32 SD vs 0.14 SD)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 ± 3.7 y (range 4–18)</td>
<td></td>
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<td></td>
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<tr>
<td>Bishop et al, 53 2013</td>
<td>Risedronate vs placebo for 1 y</td>
<td>n = 143</td>
<td>47% decrease</td>
<td>No difference</td>
<td>Increased (gain of 16.3% vs 7.6%)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.8 ± 3.4 y (range 4–15)</td>
<td></td>
<td></td>
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<td><strong>Intravenous bisphosphonate randomized trials</strong></td>
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</tr>
<tr>
<td>Letocha et al, 54 2005</td>
<td>Pamidronate vs no treatment for 1 y</td>
<td>n = 18</td>
<td>Decreased upper but not lower extremity fractures</td>
<td>Increased vertebral height</td>
<td>Increased (gain of 1.4 SD vs no change)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.1 ± 2.4 y (range 7–13)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gatti et al, 55 2005</td>
<td>Neridronate vs no treatment for 1 y</td>
<td>n = 66</td>
<td>No difference in percentage of subjects with fractures, 64% reduction in total number of fractures</td>
<td>Increased vertebral area</td>
<td>Increased (gain of 18%–25% vs 3.5%–5.7%)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7 ± 2.3 y (range 6–11)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Bisphosphonate comparison randomized trials</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>DiMeglio et al, 56 2006</td>
<td>Alendronate vs pamidronate for 2 y</td>
<td>n = 18</td>
<td>No difference between groups</td>
<td>n/a</td>
<td>No difference between groups (gain of 2.1 SD vs 1.9 SD)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7 y (range 3–17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barros et al, 57 2012</td>
<td>Pamidronate vs zoledronic acid</td>
<td>n = 23</td>
<td>Decrease in fracture rate in both groups compared with baseline with no difference between groups</td>
<td>n/a</td>
<td>Greater gain in zoledronic acid group (gain of 2.5 SD vs 1.5 SD)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.6 ± 4.5 y (range 1–16)</td>
<td></td>
<td></td>
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</tbody>
</table>

**Abbreviations:** BMD, bone mineral density as measured by dual energy radiographic absorptiometry; n/a, not assessed; SD, standard deviation.
bone mineral density either alone \textsuperscript{66} or in combination with bisphosphonate treatment \textsuperscript{67} but has not been demonstrated to decrease fracture rate. Currently there is insufficient evidence to support the standard use of growth hormone in children with OI.

**Potential future therapies**

Receptor activator of nuclear factor-κB ligand inhibitors, such as denosumab, inhibit osteoclast formation and bone degradation. In a mouse model of OI, denosumab increased bone density and cortical thickness and decreased fracture rate.\textsuperscript{68} There has been one study in 4 children with type VI OI, which demonstrated denosumab normalized previously elevated markers of bone resorption.\textsuperscript{69} Further data of its effect on fracture rate and bone pain in children with OI are still needed.

Antisclerostin and Dickkopf-1 antibodies increase osteoblast activity and periosteal bone formation through inhibition of the Wnt pathway.\textsuperscript{70} Sclerostin antibody treatment in mice models of OI have shown improvement in long bone fragility\textsuperscript{71} and may offer a potential new therapy option for children with OI in the future.

The current pharmacologic agents do not correct the primary underlying cause of OI. There is ongoing work looking at gene and molecular therapy options. Approaches in animal models that have been trialed include down-regulating the expression of the defective collagen allele through short interfering RNAs or ribozymes.\textsuperscript{72} Infusions of mesenchymal stem cells with osteoblast potential have lead to improvements in bone phenotypes in mice models of OI.\textsuperscript{73} Minimal benefits, however, were seen in a small group of children with severe OI who were given a bone marrow transplant indicating much more research is still needed in this area before clinical application.\textsuperscript{74}

**SUMMARY**

The last 10 years have led to substantial advances in the understanding of underlying mechanisms, genetics, and potential treatment options for children with OI. Management involves a multidisciplinary approach with rehabilitation, surgical management, and consideration of bisphosphonate therapy. Further research is still needed to clarify uncertainties around treatment duration and schedule, as well as to explore alternative more targeted therapeutic modalities.

**REFERENCES**


Evaluation and Treatment of Osteogenesis Imperfecta


