

# Osteogenesis Imperfecta

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## Abstract

Osteogenesis imperfecta is a common heritable connective tissue disorder. Nearly ninety percent are due to Type I collagen mutations. Type I-IV are autosomal dominant, and Type VI–XIII are autosomal recessive. They are Graded 1-5 based on severity. Genomic testing is done by collagen analysis from fibroblasts. The mainstay of treatment is bisphosphonate therapy. The prognosis is variable.

**Keywords:** Bisphosphonate, collagen, osteogenesis imperfecta

## INTRODUCTION

Osteogenesis imperfecta (OI) (brittle bone disease) is the most common heritable disorder of connective tissue.<sup>[1]</sup> Major clinical forms of OI represent quantitative and qualitative abnormalities of Type I collagen, the most abundant protein in bone.<sup>[1]</sup>

## HISTORY

A partially reconstructed skull of an Egyptian mummy was consistent with an infant affected by OI. The flattening of the vertical axis and widening of the transverse axis in the mummy were consistent with a tam-O-shanter deformity. There was also deformed dentition (dentinogenesis imperfecta) and thin bones.<sup>[2]</sup> Earliest studies on OI were done by Olof Jakob Ekman in 1788.<sup>[3]</sup> In 1833, Jean Lobstein described osteogenesis imperfecta Type I as “Lobstein’s disease.”<sup>[3]</sup> In the 1850s, Willem Vrolik also described what is currently known as Vrolik’s syndrome.<sup>[2]</sup>

## EPIDEMIOLOGY

The estimated incidence is approximately 1 per 20,000 live births.<sup>[4]</sup> Persons with OI caused by collagen mutations have 50% risk of having an affected child. The proportion of cases caused by a de novo mutation varies by disease severity: they include approximately 60% of cases of classic non-deforming OI with blue sclerae or common variable OI with normal sclerae, virtually 100% of perinatally lethal OI, and

close to 100% of progressively deforming OI are denovo mutations.<sup>[5]</sup> The inherited recessive disorder is less at 25% affection; however, it is more serious.

## ETIOPATHOGENESIS AND CLASSIFICATION

Collagen fibers are usually oriented in a preferential direction with hydroxyapatite crystals located in ground substance within these fibers. Hydroxyapatite crystals provide mechanical rigidity and strength to bone whereas collagen fibers provide resilience. Individuals with OI have less or poorer quality (or both) Type I collagen than unaffected people, causing their bones to deform or fracture (or both). The nosology for OI was devised by Silience *et al.* in 1979.<sup>[6]</sup> However, DNA-based findings have subsequently provided critical information concerning the genetic transmission patterns, especially for the severe forms, by revealing that autosomal dominant (AD) inheritance explains most OI patients.<sup>[7]</sup>

## CLASSIFICATION

In 2009, the International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton (INCDS) proposed that the OI syndromes are classified as five

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10.4103/ijem.IJEM\_220\_17

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**How to cite this article:** Sam JE, Dharmalingam M. Osteogenesis imperfecta. Indian J Endocr Metab 2017;21:903-8.

different groups based on phenotype alone. Under INCDS, the individual OI disorders still retain their original Roman identification but are also classified with an Arabic numeral that indicates a unifying phenotypic description [Table 1].<sup>[8]</sup>

OI is of 1-XIII Types, 1-V are AD and VI to XIII are autosomal recessive (AR). In AD, the defect is in COL1A1 and COL1A2. In Type I, the defect is in COL1A1 gene resulting in decreased production of Type I collagen, in Type II to IV have defects in COL1A1 and COL1A2 genes which lead to abnormal Type I collagen production. OI Type V has IFITM5 gene mutation which results in dysregulation of collagen mineralization.

Of the recessive forms, Type VI has SERPINF1 gene mutation leading to a mineralization defect. OI Type VII (CRTAP gene), Type VIII (LEPRE1 gene), and Type IX (PPIB gene) all results in collagen 3 hydroxylation defects. OI Type X and XI has a mutation in SERPINH1 and FKBP10 genes, respectively, resulting in chaperone defects. SP7 gene mutation is responsible for OI Type XIII and manifests as impaired osteoblast differentiation.

The genetic defects in OI translate into defects in collagen synthesis, structure, processing, in collagen posttranslational modification, collagen folding, and crosslinking. There are also defects in bone mineralization, osteoblast defect with collagen insufficiency.

## CLINICAL FEATURES

The clinical features can be broadly classified into skeletal and extraskeletal. Skeletal features include excess/atypical fractures, short stature, scoliosis, and basilar skull deformities. Extraskeletal manifestations include hearing loss which is a mixture of conductive and hearing loss and seen in 50% of adults by 50 years and in 5% of children with OI. Abnormal dentin leading to the appearance of small deformed teeth and which are opalescent due to a higher ratio of transparent enamel to opaque dentin is called dentinogenesis imperfecta and along with malocclusion are the major dental abnormalities. The sclera may be blue or gray in color. Connective tissue abnormalities leading to joint hyperextensibility may result in dislocation of joints and the head of the radius. Hypercalciuria seen in 36% of patients may result in renal calculi. Cardiovascular involvement leads to aortic root dilatation and mitral valve prolapse. Neurological manifestations include macrocephaly, hydrocephalus, basilar invagination (will present as headache, lower cranial nerve palsies, dysphagia, quadriplegia, ataxia, and nystagmus) and cervical spine kyphosis (can cause compression of cervical spine cord, sensory or motor disturbances of upper or lower extremities progressing to quadriplegia).

### Type I

The skeletal manifestations include vertebral fractures and are usually not associated with deformities can lead to scoliosis. Fractures are mostly prepubertal, associated with extraskeletal defects of blue sclera, presenile deafness, and aortic regurgitation.

**Table 1: The International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton 2009**

New OI classification/OI type	Phenotype
1/I	Mild, nondeforming
2/II	Severe, seen as perinatal and lethal forms
3/III, VI, VIII, IX, X, Bruck syndrome Type 1	Moderately severe, progressively deforming
4/IV, IV, VII, XI, XII, XIII	Moderate
5/V, osteoporosis-pseudoglioma syndrome, idiopathic juvenile osteoporosis, Bruck syndrome Type 1 and Type 2	Moderate, calcification of the interosseous membranes seen
OI: Osteogenesis imperfect	

### X-ray features

Skull shows Wormian bones and back reveals codfish vertebrae (adults). Extremities show thin cortices. Osteopenia is present.

### Type II

It is associated with *in utero* fractures – rib, long bone, and skeletal fractures. They occur in the neonatal/perinatal period, and death can occur due to pulmonary hypoplasia, respiratory insufficiency, central nervous system malformations, and hemorrhages. They also have blue sclera and dentinogenesis imperfecta.

### X-ray features

Skull shows undermineralization with plaques of calcification and back reveals platyspondyly. Extremities are severely deformed; broad, crumpled and bent femurs are seen. Small beaded ribs are pathognomonic of IIA and pectus excavatum in IIB.

### Type III

Manifestations can start *in utero* or at birth, can lead to progressive deformity and scoliosis. The sclera is blue at birth but whitens with age and has dentinogenesis imperfecta. They survive the neonatal period but have triangular facies, short stature, severe long bone deformities, may have respiratory insufficiency from pulmonary hypoplasia, fractures, and frequent hearing loss.

### X-ray features

Skull shows Wormian bones, frontal bossing, and micrognathia and back reveals codfish vertebrae, kyphoscoliosis, and platyspondyly. Extremities show flared metaphyses (“popcorn-like” appearance [childhood]), bowing, and thin cortices. Other features include thin ribs, severe osteoporosis by dual-energy X-ray absorptiometry (DEXA).

### Type IV

They can present at birth and can have progressive deformity. They have grayish or white sclera, have dentinogenesis imperfecta. They can have significant variability in phenotypes even within families and manifest with short stature, may have long bone bowing, scoliosis, and joint laxity.

### X-ray features

Skull may or may not show Wormian bones. Back reveals codfish vertebrae. Extremities show thin cortices. Other features include protrusio acetabuli.

**Type V**

They have fractures and can lead to hypertrophic calluses and are associated with progressive deformity. Irregular mesh-like bone appearance and calcification of the interosseous membranes of the forearm can lead to decreased hand mobility and radial head dislocation.

*X-ray features*

Skull shows relative macrocephaly and Wormian bones. Back reveals mild-to-moderate scoliosis. Extremities show hypertrophic callus, usually of the femurs; mineralization of the interosseous membrane in the forearm; and radiopaque metaphyseal bands adjacent to growth plates. Other features include severe osteoporosis by DEXA.

**Type VI**

Manifestations include moderate-to-severe deformities. They may have blue sclera. They are healthy at birth with subsequent progressively severe deformities. Undermineralization and “fishscale” pattern on iliac crest biopsies are observed.

*X-ray features*

Skull shows Wormian bones. Back reveals scoliosis and compression fractures. Extremities are similar to OI Type IV; bulbous metaphyses. Other features include severe osteoporosis by DEXA, coxa vara, and protrusio acetabuli.

**Type VII**

Manifestations include moderate-to-severe deformities. They may have blue sclera. Rhizomelia of humerus and femur is seen. This type has only been identified in Native Americans in Northern Quebec.

*X-ray features*

Skull shows often small head circumference and Wormian bones. Back reveals severe scoliosis. Extremities are similar to OI Type IV and also show popcorn metaphyses, severely under tubulated long bones. Other features include rhizomelic shortening, osteopenia, and coxa vara.

**Type VIII**

They have progressive deformities. They also have rhizomelia and short stature.

*X-ray features*

Skull shows open sutures, normal to small head circumference. Back reveals severe scoliosis and could be similar to OI Type II/III. Extremities show popcorn metaphyses and severely under tubulated long bones. Other features include severe osteoporosis by DEXA; thin ribs, barrel-shaped chest, and rhizomelia.

**Type IX**

Severe deformities and blue sclera are seen. They may have short stature.

*X-ray features*

Skull shows Wormian bones. Back reveals kyphoscoliosis and may not have compression fractures and a range of skeletal features similar to OI Type II/III/IV. Extremities show

bowed limbs. Other features include pectus carinatum, pectus excavatum, and moderate-to-severe osteoporosis by DEXA.

**Type X**

Severe deformities and blue sclera are seen. They also have renal stones.

**Type XI**

Severe deformities are seen. They have contractures.

**Type XII**

They have recurrent fractures and mild bone deformities and delayed tooth eruption.

**Type XIII**

They have recurrent fractures and have hyperextensible joints. They also have high bone mass.

**INVESTIGATIONS**

Clinical diagnosis of OI is based on the signs and symptoms. Diagnosis is usually straightforward in individuals with bone fragility and a positive family history or several extraskeletal manifestations.<sup>[9]</sup> Skeletal conditions resembling OI are shown in Table 2.

There are no definitive tests for OI. Biochemical parameters of bone and mineral metabolism are usually normal in OI; serum alkaline phosphatase may be increased in Type VI OI, due to impaired bone mineralization.<sup>[10]</sup> Hypercalciuria is common in OI children; the magnitude reflects severity of skeletal disease.<sup>[11]</sup> Markers of bone formation (C-terminal propeptide of Type I procollagen) may be lower, and markers of bone resorption (C-telopeptide of Type I collagen) can be higher in OI, particularly in severely affected patients.<sup>[12]</sup> Collagen synthesis analysis is performed by culturing dermal fibroblasts obtained during skin biopsy. Abnormalities either in quantity or quality of Type I collagen are found in 90% of OI.

Prenatal DNA blood testing for gene defects shows accuracy of 60%–94%, can be obtained by analyzing uncultured chorionic villus cells obtained by ultrasonography (USG).

Prenatal USG is most useful in evaluating OI Types II and III and is capable of detecting limb-length abnormalities at 15–18-week gestation. In its most severe form, the disease may be evident as early as 16-week gestation.<sup>[13]</sup> Mild forms of OI may result in normal findings on USG.

**PLAIN RADIOGRAPHY**

Plain radiographs may depict the following three radiologic categories of OI:

- Category I – Thin and gracile bones
- Category II – Short and thick limbs
- Category III – Cystic changes.

The following features may be seen:

- Fractures – Commonly, transverse fractures and those affecting the lower limbs

- Excessive callus formation with popcorn bones - Multiple scalloped, radiolucent areas with radiodense rims
- Skull changes - Wormian bones, enlargement of frontal and mastoid sinuses, and platybasia with or without basilar impression
- Deformities of the thoracic cage - Fractured and beaded ribs and pectus carinatum
- Pelvic and proximal femoral changes - Narrow pelvis, compression fractures, protrusio acetabuli, and shepherd's crook deformities of the femurs
- Densitometry - DEXA can be used to assess bone mineral density (BMD) in children with milder forms of OI. BMD, as measured with DEXA, is low in children and adults with OI regardless of severity. In infants with OI, bone mineral densities can be normal even in severe cases
- Other tests - Polarized light microscopy or microradiography may be used in combination with scanning electron microscopy to assess dentinogenesis imperfecta. Bone biopsy may show changes in concentrations of noncollagenous bone proteins such as osteonectin, sialoprotein, and decorin
- Differential diagnosis: OI needs to be differentiated from other disorders of bone and collagen [Table 2].

**TREATMENT**

The goals of therapy are to reduce fracture rate, prevent long bone deformities, minimize chronic pain, and maximize functional capacity.<sup>[14]</sup>

The main modalities of treatment can be grouped into medications, surgical intervention, physical therapy, and experimental therapies.<sup>[15]</sup>

**Bisphosphonate therapy**

It is the mainstay of pharmacologic fracture prevention therapy for most forms of OI. Observational studies show that bisphosphonates for children reduced fracture frequency up to 100%.<sup>[16]</sup> The long-term effects on structural outcomes such

as scoliosis and basilar invagination are unclear. Optimal dose range, dosing interval, duration of treatment, and long-term efficacy and safety profile in treatment of OI are yet to be established.<sup>[17]</sup> Fourteen randomized controlled trials have been conducted which compared the following data:<sup>[18]</sup> 6 - oral bisphosphonate to placebo, 3 - intravenous (IV) bisphosphonate to placebo, 1 - different doses of oral, 1 - different doses of IV, 1 - oral versus IV, and 2 - different IV (zoledronic vs. pamidronate).

**Intravenous pamidronate**

For patients with all forms of OI, IV pamidronate is advised, except Type VI, in whom clinical benefits are likely to outweigh potential long-term risks (i.e., those with long bone deformities, vertebral compression fractures, and ≥3 fractures/year) Majority of information about the use of bisphosphonates in OI have come from uncontrolled studies of cyclical infusions of pamidronate in various regimens in children.<sup>[19]</sup> Reports have noted BMD, decreased fracture rate, and improved functional abilities, mobility, ambulation, and pain, without negative effects on fracture healing or growth rate in most studies, even when used in young children. Pamidronate is administered IV in cycles of 3 consecutive days at 2–4-month intervals with doses ranging from 0.5–1 mg/kg/day, depending on age, with a corresponding annual dose of 9 mg/kg. Smallest effective dose should be used, with careful monitoring of vertebral geometry, long-bone fractures, and BMD before initiating a new cycle of treatment.

**Intravenous zoledronic acid**

Safety and efficacy of zoledronic therapy was evaluated over 2 years, among 33 children with OI, showed reduction in fracture rates, pain, and improvement in BMD and motor milestones of development and dose - 0.1 mg/kg ZA.<sup>[20]</sup>

**Pretreatment evaluation and monitoring**

There are no written guidelines or protocols. Calcium and vitamin D intake are based on recommended dietary allowance for child's age (700–1300 mg/day calcium and 400–600 IU vitamin D) should be supplemented before treatment is initiated if dietary intake is inadequate. Indices of calcium homeostasis (e.g., calcium, phosphorous, and parathyroid hormone) and renal function test should be assessed before initiation of treatment and followed every 6–12 months. Calcium levels are to be assessed before each IV bisphosphonate infusion to assure that child is not hypocalcemic.

**Orthopedic and other surgery**

Management of fractures (with quick mobilization to prevent bone loss due to inactivity) and placement of intramedullary rods to prevent or correct long-bone deformities are advised. Telescoping rods is advised for patients older than >2 years who are actively growing. Those with severe scoliosis may benefit from surgery.

**Physical and occupational therapy**

Physical therapists are instrumental in designing physical activity program that minimizes fracture risk, ensuring

**Table 2: Skeletal conditions resembling osteogenesis imperfecta<sup>[29]</sup>**

Condition	Genes	Disease mechanism
Osteoporosis pseudoglioma syndrome	LRP5	Impaired Wnt signaling and osteoblast function
Bruck syndrome	PLOD2	Impaired collagen crosslink formation
Ehlers-Danlos syndrome	COL5A1, COL5A2, TNXB, COL3A1	Connective tissue defects
Hypophosphatasia	ALPL	Defective bone mineralization from low alkaline phosphatase activity
Idiopathic hyperphosphatasia	TNFRSSFIIB	Excessive bone resorption and formation
Idiopathic juvenile osteoporosis	Unknown	Unknown

mobilization to prevent contractures and bone loss from immobility.<sup>[21]</sup> Occupational therapists can address impairments in activities of daily living secondary to upper or lower limb deformities.

## EXPERIMENTAL THERAPIES

### Growth hormone

In a single randomized trial, thirty prepubertal children with OI (Types I, III, and IV) were observed for 12 months during ongoing neridronate therapy and then randomized to recombinant growth hormone (GH) plus neridronate or neridronate alone. BMD and growth velocity were found to be significantly higher in the group that received GH compared with control group, but no differences were observed in the fracture risk.<sup>[22]</sup>

### Cell replacement therapies

Pilot study of allogeneic hematopoietic cell transplantation was performed in five children with OI; three children had successful engraftment, and in these 3, improvements in growth velocity and reduction in fracture rate were noted following transplantation.<sup>[23]</sup> More clinical research is needed for exploring this modality.

### Gene therapy

It has been performed only in animal models by two techniques. Antisense therapy has been used to suppress or silence a particular mutant allele of Type I collagen gene and not interfere with expression of normal allele, and thus, a severe form has been potentially turned into mild form.<sup>[24]</sup> Gene targeting has been employed using patient's mesenchymal stem cells. A preliminary study using adeno-associated virus vectors successfully disrupted mutated allele *ex vivo* in these cells and infusion into a mouse model resulted in bone formation.<sup>[25]</sup>

### Recent advances

Strontium ranelate and denosumab targeting RANKL pathway are being studied for use in OI.

### Psychosocial aspects

Support for patients with OI and families can be availed by provision of information, contact with other patients and families, and referrals for formal or informal counseling.<sup>[26]</sup>

### Primary care considerations

Primary care of OI children requires special considerations in addition to routine care and immunizations. Hearing assessment (formal audiology) should be advised initially at 9 months of age and then at regular intervals. Vision screening should be done every 2–3 years, with referral to an ophthalmologist. Pneumococcal and influenza vaccination needs to be emphasized.<sup>[27]</sup> Provision of dental referral is to be done as indicated for dentinogenesis imperfecta.

### Monitoring for complications

At 2 years, hearing test for mixed hearing loss, DEXA for BMD,<sup>[28]</sup> and spirometry to monitor for restrictive

defects secondary to rib and vertebral fractures (or sooner if clinically indicated), particularly in patients with moderate-to-severe OI has to be done. Yearly spirometry and electrocardiogram/echocardiogram every 2 years (to detect aortic root dilation and valvular dysfunction) in Type III OI or other moderate-to-severe types are to be done. Neurologic examination and cranial assessment should be performed if symptoms or behavioral changes, particularly in patients with Type III OI and in other forms with a similar phenotype (Types VII–IX). At diagnosis and then every 1–2 years, skeletal radiographs (or sooner if clinically indicated) coordinated with orthopedic advice needs to be monitored. Children receiving bisphosphonate treatment should have yearly (or more frequently as clinically indicated) assessment of BMD and radiologic assessment of long bones and spine to determine the effect of treatment on vertebral geometry, long-bone fractures, and changes in bone mass.

## CONCLUSION

OI is the most common heritable connective tissue disorder. 90% due to Type I collagen mutations. Types I to V are AD and VI–XIII are AR. Genomic testing is useful for collagen analysis from fibroblasts and the prognosis is variable.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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