Introduction

- Osteogenesis Imperfecta (OI) is an inherited disorder of type I collagen characterised by bone fragility and low bone mass.
- Severity varies widely, ranging from intrauterine fractures and perinatal death to very mild forms without fractures.
- Typical extra-skeletal manifestations are also associated variably with the disorder, and these include blue sclerae, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment, and presence of wormian bones on skull radiographs (see Tables 1 and 2).
- This article reviews the clinical manifestations, classification, pathogenesis and management of OI (Figs. 1–3).

Clinical features

- Radiographic features: Diffuse osteopenia associated with multiple fractures and deformities.
- Histopathologic features: Generalised decrease in bone tissue.

Epidemiology and genetics

- The incidence of OI is about 1 in 20,000, and it occurs equally among males and females and in all racial and ethnic groups.
- Most cases of OI (types I–IV) are caused by an autosomal dominant genetic mutation, and in most instances (about 90%), this is in one or two of the genes that encode the \( \alpha \)-chains of collagen type 1 (COL1A1 and COL1A2).
- Little is known about the pathogenesis of types V–VII.
- COL1A1 and COL1A2 are large genes (located on chromosomes 17 and 7, respectively) that have been associated with over 200 mutations in OI patients.\(^3\)
- A collagen type 1 molecule consists of three polypeptide chains (two alpha 1 and one alpha 2 chain) that intertwine via a glycine residue at every 3rd position so forming a triple helical structure.\(^4\)
- The mutations can be divided into two categories:\(^5\)
  1. **Excluded**: mutations that result in the exclusion of the product of the mutant allele from the mature collagen molecule,
  2. **Included**: those that permit the incorporation of a structurally abnormal chain.

Exclusion: Type 1 (non-deforming OI)
In most cases this phenotype is caused by a mutation that creates a premature stop codon within COL1A1. This results in a null COL1A1 allele,\(^6\) which, as a consequence of nonsense-mediated decay, destabilises the mRNA and leads to only half the normal amount of type I pro-collagen being synthesised by the fibroblasts of affected individuals.\(^7\)

Inclusion: Type II–IV (deforming OI)
These mutations generate abnormal type I pro-collagen molecules that are more deleterious than those of null mutations. The most typical sequence abnormality is a point substitution mutation that affects a glycine residue in either COL1A1 or COL1A2,\(^7\) the phenotypic consequences of which,
Therefore in patients expressing this mutation, bone formation is defective because of paucity of type I collagen, thereby making it plausible that agents that augment collagen production have a beneficial effect.\(^7\)

(2) the position in the triple helix at which the substitution arises

(3) which amino acid is substituted for glycine

The consequence of such mutations is high bone turnover,\(^8\) and therefore agents that limit degradation might augment bone formation.

- It is likely that the phenotypic variations between affected individuals are attributable to unknown environmental and genetic factors that modify the expression of the mutant collagen allele.

### Classification

- The most widely used classification of OI is by Sillence and colleagues,\(^9\) which distinguishes four clinical types (OI type I–IV) based on clinical, radiological and genetic data.
- Recently a new group of patients has been identified at the clinical and molecular level and added to the present classification as OI type V–VII.\(^10–12\)

#### Type I

- This is the most common form and includes patients with mild disease and absence of major bone deformities.
- It is sub-classified into:
  1. Type A (without dentinogenesis imperfecta),
  2. Type B (with dentinogenesis imperfecta).
- The sclerae are blue and most fractures occur before puberty.
- Vertebral fractures are typical and can lead to mild scoliosis.
- Hearing loss occurs in about 50% of families and women are twice as often affected as males.
- Connective tissue malfunction, such as thin skin, hernias and generalised joint hyper-mobility, are present.
- A delay exists in achieving motor milestones, but children with OI type I do have normal intelligence and life expectancy is normal.

#### Type II

- This is lethal in the perinatal period, usually because of respiratory failure resulting from multiple rib fractures.
- Narrow thoraces, short and deformed extremities with multiple fractures, and a typical frog-like position are the main features.\(^13\)
- Newborns have soft calvarial bones, distinctive triangular faces, bluish sclerae, and beaked noses.
- Survival beyond a year is very rare.\(^14\)

#### Type III

- This occurs in approximately 20% of all patients with OI.
- It is the most severe form in children surviving the neonatal period.
These patients are of very short stature and have limb and spine deformities secondary to multiple fractures, which can lead to respiratory difficulties (identified as the leading cause of death in this patient group).

The sclerae are frequently normal but a significant number have large and asymmetric heads, while the face is triangular.

The maxilla is frequently posteriorly inclined and dental malocclusion occurs in 80%.

Muscle strength and muscular imbalance are poor.\(^{13}\)

Life expectancy is decreased, but affected individuals live into adulthood.

**Type IV**

- This is usually intermediate in severity between types I and III.
- Patients exhibit mild to moderate bone deformities, variable short stature, dentinogenesis imperfecta and greyish sclera.

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**Figure 1**  OI patient, wheelchair bound with short stature in this case.

**Figure 2**  Thoracic scoliosis.
Type V

- Heredity seems to follow an autosomal dominant pattern but there remains no evidence of a collagen type 1 abnormality.
- Patients have normal sclerae and no dentinogenesis imperfecta.
- The interroseous membrane at the forearm becomes calcifies early in life, which severely limits movement and can lead to secondary dislocation of the radial head.
- Importantly, after fractures or surgical interventions, patients are predisposed to develop hyperplastic callus, which can mimic osteosarcoma. 

Type VI

- This is defined on the basis of bone histological findings, which show a higher amount of osteoid than usual and an abnormal ‘fish scale’ pattern of lamellation suggestive of disordered mineralisation of bone tissue, even though concentrations in serum calcium and phosphorus are normal.

Type VII

- This is a moderately deforming recessive disorder that so far has only been reported in a community of Native Americans in northern Quebec.
- Apart from bone fragility, rhizomelia is a prominent clinical feature, and coxa vara can be present in infancy.
- The disease has been localised to chromosome 3p22–24.1, which is outside the loci for collagen type 1 genes.

Differential diagnosis

- There are many skeletal dysplasias which resemble OI, but the main differential diagnosis in a child presenting with multiple unexplained fractures is child abuse, especially if the family history is negative for the disorder.

Management

Aims of non-surgical management:
- Reduce fracture rates
- Prevent long bone and spinal deformities
- Improve functional outcome

Physiotherapy, rehabilitation and occupational therapy

This is an important element of the multi-disciplinary approach to the management of OI.

Medical therapy

Bisphosphonates. These anti-resorptive agents interfere with the cholesterol biosynthesis of osteoclasts therefore inhibiting these cells but not leading to apoptosis.

Pamidronate

- This is the most widely used, second generation bisphosphonate.
- A study by Glourieux et al., has reported successful treatment with pamidronate; there was a reduction
in fracture rate, increased bone mineral density and increased vertebral coronal area in the treated patients.

- Administration of bisphosphonates should be achieved as early as possible and a trial by Sokby et al., found that if pamidronate was used in combination with surgery, the bone mineral density would increase and rate of re-fracture would decrease. Thus the best form of management is to use pamidronate in combination with surgery, pre and post-operatively.

- However there remains controversy over who should receive bisphosphonate treatment since the long-term effects have not yet been discovered. The concerns arise because bisphosphonates remain buried in the skeleton where they have a half life of many years.

- They may therefore interfere with bone remodelling during growth and have a possible adverse effect on future pregnancies when the drug is given to pre-menopausal girls.

- The drawback to pamidronate treatment is the inconvenience of having the drug intravenously infused every few months and therefore oral bisphosphonate therapy (e.g. alendronate) is now being researched.

**Alendronate**

- Recent trials have found that oral alendronate (a more potent bisphosphonate than pamidronate) increases bone mineral density in both children and adults, but more studies are required to evaluate the effects on fracture rates.

- Since bone mineral density appears to be an indicator of disease severity and may be predictive of long term functional outcome, it seems likely that agents such as bisphosphonates would improve function, decrease rates of fracture and the need for surgery.

**Analgesia**

Fracture and non-fracture pain can pose a significant burden for the children and their families, and therefore adequate pain management is essential.

**Bone marrow transplantation**

Multipotential stromal cells can be isolated from bone marrow and made to differentiate into a variety of cell types, including osteoprogenitor cells. Transplantation from an HLA identical or single-antigen mismatched sibling may ameliorate the course of severe OI. Transplanting bone marrow stromal cells from healthy people to OI patients will lead to the cells differentiating into osteoblasts and producing normal bone.

**Surgical therapy**

**Intra-medullary rods**

These are used to stabilise bone and correct deformities. The choice of intra-medullary device is important. A retrospective trial by Joseph et al., found dual Rush rods and Sheffield telescoping rods in the femur, to be equally effective and superior to a single Rush rod. In contrast, the preferential choice of rod in the tibia is a single Rush rod (Fig. 4).

**Correction of scoliosis**

This may be very difficult because of bone fragility.

**Gene transplantation**

Curing the disease is by elimination of the mutated gene or gene product. Most severe cases are due to the presence of abnormal collagen molecules. Therefore the mutant allele needs to be initially inactivated and substituted for its product. More research still needs to be carried out.
References


