# Osteogenesis imperfecta

**Author: Doctor Guillaume Chevrel[1]**
**Creation Date: October 2002**
**Update: June 2004**

**Scientific Editor: Doctor Martine Le Merrer**

[1]Service de rhumatologie et de pathologies osseuses, CHU Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon Cedex 3, France. Guillaume.CHEVREL@wanadoo.fr



**Abstract**
*Osteogenesis imperfecta (OI) is a group of inherited diseases responsible for varying degrees of skeletal fragility. Minimal trauma is sufficient to cause fractures and bone deformities. A classification with 5 types is most widely used.*
*Type I: moderate form with autosomal dominant transmission, characterized by blue sclerae or dentinogenesis imperfecta and sometimes late hearing loss, but no growth retardation.*
*Type II: lethal form, with autosomal dominant transmission.*
*Type III: severe form with autosomal dominant or recessive transmission, characterized by blue sclerae and dentinogenesis imperfecta.*
*Type IV: intermediate form with autosomal dominant transmission, characterized by normal sclerae and with or without dentinogenesis imperfecta.*
*Type V: form with hypertrophic calluses and calcification of interosseous membrane.*
*Type V does not seem to be related to the* COL1A1 *or* COL1A2 *genes.*
*OI is caused by mutations in the* COL1A1 *or* COL1A2 *gene, which encode the alpha1 and alpha2 chains of type 1 collagen, respectively. These mutations are responsible for the production of quantitatively or qualitatively deficient fibrils. Accurate incidence and prevalence of the disease are currently unknown. The diagnosis is often readily made in infancy; some cases, however, go unrecognized until adulthood. Lifelong multidisciplinary management is imperative. Pamidronate therapy in childhood is the most extensively studied treatment and has been proved beneficial. Prevention of vitamin D and calcium deficiency is essential throughout life. Various orthopedic and surgical techniques are available for reducing the fractures and correcting the deformities. Pain is common and should be given adequate attention.*

**Keywords**
Osteogenesis imperfecta, trauma, fracture, bone deformities, blue sclerae, dentinogenesis imperfecta, *COL1A1* or *COL1A2*, Pamidronate, vitamin D and calcium supplementation

**Disease name and synonyms**
-Osteogeneis imperfecta
-Glass bone disease (1)
-Brittle bone disease
-Lobstein's disease (2)
-Porak and Durante's disease (3)

**Definition/Diagnosis criteria**
Osteogenesis imperfecta (OI) is a group of orphan diseases characterized by varying degrees of skeletal fragility. Fractures and bone deformities occur with trivial trauma. The most widely used system to classify the different types of OI is developed by Sillence *et al.* (4,5). It is based of clinical, genetic and radiographic findings:
-Type I: the most common form, is autosomal dominant and is characterized by blue sclerae, a typical feature of OI (6). The number of fractures is fairly small and the deformities are modest, causing little loss of stature.
-Type II: which is also autosomal dominant, is the lethal form of the disease. The sclerae are blue and death is due primarily to lung underdevelopment caused by rib fractures.
-Type III: is autosomal dominant or recessive (7) and is the most severe non-lethal form. The sclerae are white, the face triangular, and the fractures commonly accompanied with progressive deformities and short stature.
-Type IV: is autosomal dominant and usually characterized by white sclerae, short stature, and skeletal deformities that are less severe than those in type III. Type IV is the most heterogeneous group because it comprises those patients who do not meet the criteria for the other three types.
-Type V: characterized by hypertrophic calluses, sometimes mistaken for osteosarcomas, and by ossification of the interosseous membranes (8). Type V does not seem to be related to the *COL1A1* or *COL1A2* genes.
Although widely accepted, many patients with OI do not readily fall into Sillence's classification due to the broad spectrum of molecular abnormalities resulting in OI. This has prompted some investigators to propose existence of other subtypes of OI believed not to be directly associated with type I collagen mutations but other yet unidentified macromolecules (32): **Type I Mild, non-deforming**, due to premature stop in *COL1A1*, autosomal dominant inheritance, characterized by normal height or mild short stature, blue sclera, no dentinogenesis imperfecta. **Type II Perinatal lethal**, autosomal dominant inheritance; glycine substitutions in *COL1A1 or COL1A2*: Multiple rib and long bone fractures at birth, severe skeletal deformities, dark sclera. **Type III Severely deforming:** autosomal dominant; glycine substitutions in *COL1A1 or COL1A2*. Very short stature, triangular face, severe scoliosis, greyish sclera, dentinogenesis imperfecta. **Type IV Moderately deforming:** autosomal dominant; glycine substitutions in *COL1A1 or COL1A2*. Moderately short stature, mild to moderate scoliosis, greyish or white sclera, dentinogenesis imperfecta. **Type V Moderately deforming:** autosomal dominant, unknown associated mutations. Mild to moderate short stature, dislocation of radial head, mineralized interosseous membrane, hyperplastic callus, white sclera, no dentinogenesis imperfecta. **Type VI Moderately to severely deforming**: autosomal dominant, unknown associated mutations. Moderately short stature, scoliosis, accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation, white sclera, no dentinogenesis imperfecta. **Type VII Moderately deforming:** autosomal recessive, unknown associated mutations. Mild short stature, short humeri and femora, coxa vara, white sclera, no dentinogenesis imperfecta (32,33).

**Differential diagnosis**
In neonates and children, the presence of fractures that occurred at various ages can suggest child abuse. However, the possibility of OI should be borne in mind: some parents of children with OI have been wrongly accused of battering their children. Consequently, when child abuse is suspected, radiological abnormalities that can point to OI should be looked for carefully. However, the radiological changes in OI are nonspecific, although the presence of wormian bones is highly suggestive. In some cases, dual-photon X-ray absorptiometry is useful in discriminating between OI, in which bone mineral density (BMD) is low, from child abuse.
Other causes of osteopenia in infants and young children include immobilization, premature birth, vitamin D deficiency, and hematological diseases.
In older children, the combination of fractures and osteoporosis during the course of a known disease raises no diagnostic problems. When the diagnosis remains in doubt, idiopathic juvenile osteoporosis (IJO) should be considered if rare causes of osteopenia (*e.g.*, leukemia) have been ruled out. In the absence of clinical evidence of OI, a diagnosis of IJO can be given. IJO is typically discovered during evaluation of a

fracture between 8 and 11 years of age (*i.e.*, before puberty) in a boy or girl (see (9) for a review of reported cases). A common feature is pain in the spine, hips, and feet, with difficult walking. The fractures are typically metaphyseal, although no segment of the long bones is exempt. Vertebral fractures are common and can result in deformities and a slight loss of height of the trunk. The skull and facial skeleton are normal. There are no characteristic biochemical abnormalities. IJO improves spontaneously within 3 to 5 years, although the vertebral deformities and functional impairment can persist. A positive family history should suggest a mild form of OI.
Other skeletal disorders resembling OI (32) that take place in the differential diagnosis of OI are:
*Hypophosphatasia* (mild to severe bone fragility/deformity; low alkaline phosphatase activity, autosomal recessive, autosomal dominant inheritance, *ALPL* defect);
*Idiopathic hyperphosphatasia* (severe bone fragility/deformity, raised alkaline phosphatase activity, autosomal recessive inheritance, *TNFRSF11B* genetic defect);
*Bruck syndrome* (moderate to severe bone fragility/deformity, congenital joint contractures, autosomal recessive inheritance; telopeptide lysyl hydroxylase deficiency);
*Cole-Carpenter syndrome* (severe bone fragility/deformity, craniosynostosis, unknown genetic defect and inheritance).

**Frequency**
Accurate incidence and prevalence data are not available. It was reported to range from one per 10 000 to one per 20 000 live births (34).

**Clinical description**
In addition to the clinical manifestations used in distinguishing the different types of OI (see chapter Definition/diagnosis criteria), several other features deserve to be underlined because they provide diagnostic orientation in patients, particularly adults, with mild bone symptoms.

Scoliosis is common. The combination of chest deformities and scoliosis is responsible for a large number of deaths due to respiratory disorders (10,11). Some forms, most notably type III, are characterized by dentinogenesis imperfecta manifesting as brittle teeth. Hearing loss, which can be sensorineural, conductive or mixed, can develop gradually, particularly in type I (deafness occurs in approximately 40% of type I patients). Ligamentous laxity is common, as are trauma-related hematomas and atrophic skin scars. Many patients have neurological abnormalities, of which the most common is basilar impression (12).

Musculoskeletal abnormalities include long bone deformities with anterior bowing of the humerus, tibia and fibula and lateral bowing of the femur, radius and ulna. The hallmark of OI is bone fragility with fractures occurring with minimal to moderate trauma. In general, the earlier the fractures occur in life, the more severe the disease is. The lower limbs are more commonly involved. Femural fractures are the most common fractures of long bones, with the fracture located usually at the convexity of the bone, usually transverse and minimally displaced. Multiple fractures within the same bone often occur. Cranial deformity is also common. There is flattening of the posterior cranium with a bulging calvarium and a triangular-shaped face (type III).

**Etiology**
OI is a group of inherited disorders caused by mutations in the *COL1A1* or *COL1A2* gene, which encode the alpha1 and alpha2 chains of type 1 collagen produced by osteoblasts, respectively (13). These genes are susceptible to many mutations responsible for the production of quantitatively or qualitatively deficient fibrils (14).
These mutations are private, *ie.* specific to a family or to an individual when they occur *de novo*.

**Diagnostic methods**
If OI is not obvious at birth, the diagnosis is often made when the child starts to walk. However, some cases go unrecognized until adulthood.
The Sillence classification scheme helps to establish the diagnosis, but only when the clinical signs are obvious. The presence of blue sclerae and a positive family history are the most reliable features, although there are exceptions, which can raise problems if a therapeutic trial is being considered.

***Histomorphometry***
In a small minority of cases the bone biopsy shows specific abnormalities, which help to establish the diagnosis of OI. The biopsies should be of excellent quality and should be examined by observers who are thoroughly familiar with OI.
Routine analysis of bone biopsies from children with OI has shown that type IV in the Sillence classification scheme encompasses a number of

specific patterns, such as type V individualized by Glorieux *et al.* (8). In comparison to normal children, the increase in trabecular width is less marked in type I and absent in types III and IV.

***Genetic diagnosis***

The diversity of the mutations involved in OI is a major stumbling block to the genetic diagnosis of OI: in theory, identification of the mutation requires that both type 1 collagen genes be analyzed. The chances of success of this analysis depend on both the clinical pattern of the disease and the technique used. Unfortunately, this analysis is not available on a routine basis and remains a research tool. Other genetic analysis techniques exist, but their applicability is partly conditional on the number of family members.

***Bone density measurement***

Although bone density measurement (BMD) is now widely available, few patients with OI have been investigated using this method. BMD is normal in a tiny number of cases, even in the absence of degenerative spinal disease or hip abnormalities (15). In most cases, however, BMD is far below the normal range, as shown by the Z-score in children and the T-score in adults (16-18). In some patients, the bone is so transparent as to interfere with image analysis by the absorptiometry device. As in osteoporosis, the low BMD is probably a major risk factor for further fractures. However, the definition of osteoporosis developed by the World Health Organization, *i.e.* a T-score lower than 2.5, has not been validated prospectively in adults with OI. Neither BMD measurement using ultrasound has been validated in patients with OI.

***Phosphate, calcium, and bone turnover markers***

Serum calcium is normal in patients with OI. Hypercalciuria has been reported in some patients in the absence of prolonged immobilization (19), with no renal dysfunction or nephrocalcinosis (20).

Serum 25-hydroxy-vitamin D is often low, indicating vitamin D deficiency secondary to lack of exposure to sunlight, which is fairly common in these patients (Meunier *et al*., 7th International Conference on Osteogenesis Imperfecta, Montreal, 1999).

Biochemical markers for bone turnover do not provide accurate information on bone structure in OI, although a selective decrease in serum levels of carboxy-terminal propeptide of type I collagen (PICP) has been reported (21-23). However, other bone turnover markers, such as osteocalcin, alkaline phosphatase, and amino-terminal telopeptide of type I collagen are useful for monitoring children with OI (24- 26).

**Management**

The management of patients with OI requires the involvement of a multidisciplinary team including general practitioners and specialists who work near the home of the patient. Indeed, this rare disease raises many problems in everyday life. Patient organizations (in France: the "Association de l'Ostéogenèse Imparfaite") play a key role in disseminating practical information about the disease (27). In some cases, management must be started at birth. The management of OI involves appropriate rehabilitation therapy directed both at the fracture and at the development of the child.

Long-term follow-up is essential in patients with OI. The annual fracture rate decreases at puberty but increases subsequently during adulthood. In women, fractures are common after the menopause as a result of the combined influence of OI and osteoporosis (28). In men, the fracture rate increase is most marked between 60 and 80 years of age.

**Treatment**

***Medications***

The ultimate goal of medical treatment in children with severe osteogenesis imperfecta should be to reduce fracture rates, prevent long-bone deformities and scoliosis, and improve functional outcome.

*Bisphosphonates*

Systematic studies have established that bisphosphonates, most notably Pamidronate, constitute a breakthrough in the treatment of OI. (24, 29). Pamidronate therapy has been shown to cause pain relief and to result in the increase of BMD and size of vertebras, as well as in a decrease of the incidence of fractures, while no adverse effects on growth were reported.

The benefits of pamidronate therapy are sufficiently impressive to suggest that routine use of this agent may be in order in all children with OI, even when the manifestations are mild, although this last point is controversial. The need for intravenous injections may limit the use of pamidronate. Studies of oral bisphosphonates (*e.g.*, alendronate Fosamax®) are ongoing in children with OI.

Hormone replacement therapy or selective estrogen receptor modulator therapy is strongly recommended in postmenopausal women with OI.
Some data show that growth hormone might be useful in combination with bisphosphonates. Parathyroid hormone as a potent bone anabolic agent could be a candidate for treating OI but both regimens remain to be tested.

*Vitamin D and calcium supplements*
The measures taken to protect patients with OI from trauma and the repeated immobilizations required by the fractures often result in vitamin D and calcium deficiency in children and adults. Prophylactic supplementation is in order, with dosages of about 500 to 1000 mg of calcium and 400 to 800 IU of vitamin D.

*Analgesics*
Pain is common and should receive adequate attention. Bone pain responds well to bisphosphonate therapy (24,26,29). Other causes of pain include deformities and degenerative lesions, both of which are common: in this situation, the treatment is symptomatic.

*Cell and gene therapies* as potential treatments for OI are currently actively investigated. The design of gene therapies for OI is however complicated by the genetic heterogeneity of the disease and by the fact that most of the OI mutations are dominant negative where the mutant allele product interferes with the function of the normal allele. Major obstacles result from the presence of abnormal collagen molecules. Techniques based on marrow stem cells are under investigation.

***Orthopedic treatment***
Orthopedic treatment remains indispensable in OI. A careful preoperative evaluation with special attention to lung function is essential in types III and IV. In children, rodding surgery is well standardized (reviewed in 30, 31). The treatment of spinal deformities varies with the angle of the scoliosis (31). After a fracture or a surgical procedure, prolonged immobilization should be avoided: rehabilitation therapy should be started early, and the healthcare staff reassured that the rehabilitation program is designed to reduce the risk of further fracturing. In children and adults, the goal of fracture management should be to restore the patient to self-sufficiency as completely and rapidly as possible.

**Genetic counselling**
Genetic counselling should be offered to the parents of a child with OI who plan to have subsequent children. During genetic counselling, the possibility that the parents may harbor new mutations, such as asymptomatic somatic and germline mosaicism, needs to be discussed. Parents need special instructions in positioning the child in the crib and handling the child with the least possibility of causing fractures. Upright sitting in infants younger than 1 year should be discouraged in order to decrease development of basilar impression later in life. Hip-knee-ankle-foot orthosis helps early achievement of upright activity.

**References**
**1**. Apert E., Les hommes de verre. Presse M 51 (1928), pp. 805-808.
**2**. Lobstein J., Von der Knochenbreichigkeit oder Osteopsathyrose. In: Lehrbuch der Pathologischen Anatomie (Bd 2 ed.),, Brodhag, Stuttgart (1835), pp.179-179.
**3**. Porak C. and Durante G., Les micromélies congénitales: achondroplasie et dystrophie périostale. Nouv Iconogr Salpêt 18 (1905), pp. 481-538.
**4**. Sillence D., Senn A. and Danks D., Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16 (1979), pp. 101-106.
**5**. Sillence D., Osteogenesis imperfecta: an expanding panorama of variants. In: ClinOrthop 159 (1981), pp. 11-25.
**6**. Leidig-Bruckner G. and Grauer A., Blue sclerae in osteogenesis imperfecta. N Engl J M 339 (1998), pp. 966-966.
**7**. Beighton P. and Versfeld G., On the paradoxically high relative prevalence of osteogenesis imperfecta type III in the Black population of South Africa. Clin Genet 27 (1985), pp. 398-401.
**8**. Glorieux F., Bishop N., Travers R., Roughley P., Chabot G., Lanoue G. *et al.*, Type V osteogenesis imperfecta. J Bone Miner Res 12 Suppl 1 (1997), pp.389-389.
**9**. Brumsen C., Hamdy N. and Papapoulos S., Long-term effects of bisphosphonates on the growing skeleton. Studies of young patients with severe osteoporosis. Medicine 76 (1997), pp. 266-283.
**10**. McAllion S. and Paterson C., Causes of death in osteogenesis imperfecta. J Clin Pathol 49 (1996), pp. 627-630.
**11**. Widmann R., Bitan F., Laplaza F., Burke S., DiMaio M. and Schneider R., Spinal deformity, pulmonary compromise, and quality of life in

osteogenesis imperfecta. Spine 24 (1999), pp. 1673-1678.
**12**. Sawin P. and Menezes A., Basilar invagination in osteogenesis imperfecta and related-osteochondrodysplasias: medical and surgical management. J Neurosurg 86 (1997), pp. 950-960.
**13**. Kuivaniemi H., Tromp G. and Prockop D., Mutations in fibrillar collagens (type I, II, III, XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of diseases of bone, cartilage, and blood vessels. Human Mutat 9 (1997), pp. 300-315.
**14**. Coppin C. and Eeckhout Y., L'ostéogenèse imparfaite: des mutations aux phénotypes. Médecine/Sciences 11 (1995), pp. 853-859.
**15**. Paterson C. and Moles P., Bone density in osteogenesis imperfecta may well be normal. Postgrad Med J 70 (1994), pp. 104-107.
**16**. Davie M. and Haddaway M., Bone mineral content and density in healthy subjects and in osteogenesis imperfecta. Arch Dis Child 70 (1994), pp. 331-334.
**17**. Glorieux F., Lanoue G., Chabot G. and Travers R., Bone mineral density in osteogenesis imparfecta. J Bone Min Res 9 (1994), pp. 225-225.
**18**. Zionts L., Nash J., Rude R., Ross T. and Stott N., Bone mineral density in children with mild osteogenesis imperfecta. J Bone Joint Surg 77B (1995), pp.143-147.
**19**. Chines A., Petersen D., Schranck F. and Whyte M., Hypercalciuria in children severely affected with osteogenesis imperfecta. J Pediatr 119 (1991), 51-57.
**20**. Chines A., Boniface A., McAlister W. and Whyte M., Hypercalciuria in osteogenesis imperfecta: a follow-up study to assess renal effects. Bone 16 (1995), pp.333-339.
**21**. Minisola S., Lina-Piccioni A., Rosso R., Romagnoli E., Pacitti M., Scarnecchia L. *et al.*, Reduced serum levels of carboxy-terminal propeptide of human type I procollagen in a family with type I-A osteogenesis imperfecta. Metabolism 42 (1994), pp. 1261-1265.
**22**. Lund A., Hansen M., Kollerup G., Juul A., Teisner B. and Skovby F., Collagen-derived markers of bone metabolism in osteogenesis imperfecta. Acta Paediatr 87 (1998), pp. 1131-1137.
**23**. Cepollaro C., Gonnelli S., Pondrelli C., Montagnani A., Martini S., Bruni D. *et al.*, Osteogenesis imperfecta: bone turn-over, bone density, and ultrasound parameters. Calcif Tissue Int 65 (1999), pp. 129-132.
**24**. Glorieux F., Bishop N., Plotkin H., Chabot G., Lanoue G. and Travers R., Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J M 339 (1998), pp. 947-952.
**25**. Shapiro J.R., Copley C., Goldsborough D., Gelman R. and Barnhart K., Effect of pamidronate on bone turnover and IGF-I in type I osteogenesis imperfecta. JBone Min Res 10 (1995), pp. 604-604.
**26**. Aström E. and Söderhäll S., Beneficial effect of bisphosphonate during five years of treatment of severe osteogenesis imperfecta. Acta Paediatr 87 (1998), pp. 64-68.
**27**. Verhaeghe P, Editor, L'ostéogenèse imparfaite, maladie des os de verre, Éditions Frison-Roche, Paris (1999).
**28**. Paterson C., McAllion S. and Stellman J., Osteogenesis imperfecta after the menopause. N Engl J M 310 (1984), pp. 1694-1696.
**29**. Plotkin H., Rauch F., Bishop N., Montpetit K., Ruck-Gibis J., Travers R. *et al.*, Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab 85 (2000), pp. 1846-1850.
**30**. Finidori G., Ostéogenèse imparfaite. Indications thérapeutiques chez l'enfant. In: Conférences d'enseignement 1988. Cahier d'enseignement de la SOFCOT n° 31, Expansion Scientifique Française, Paris (1988), pp. 327-345.
**31**. Fassier F., Ostéogenèse imparfaite de l'enfant. In: Conférences d'enseignement 1999. Cahier d'enseignement de la SOFCOT, Expansion Scientifique Publications, Paris (1999), pp. 235-252.
**32**. Rauch F., Glorieux F.H. Osteogenesis imperfecta. Lancet 363 (2004), 1377-1385.
**33**. Niyibizi C., Wang S., Mi Z., Robbins P.D. Gene therapy approaches for osteogenesis imperfecta. Gene Therapy 11 (2004), 408-416.
**34**. Engelbert R.H., Pruijs H.E., Beemer F.A., Helders P.J. Osteogenesis imperfecta in childhood: treatment strategies. Arch Phys Med Rehabil 79 (1998), 1590-1594.