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## **The management of Osteogenesis Imperfecta in Adults: state of the art**

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**ABSTRACT**

Osteogenesis imperfecta (OI) is a genetic disease whose clinical phenotype and severity vary considerably. The increased risk of fractures due to bone fragility persists in adulthood, notably after 40 years of age, albeit at a lower level than during growth. Adults with OI require periodic evaluations of the other manifestations of OI including hearing loss, respiratory impairments, ocular and dental abnormalities, and cardiovascular disease. Follow-up should therefore be provided by a multidisciplinary team, at intervals tailored to disease severity. Currently used treatments for OI have not been proven to decrease the fracture risk but are consistently effective in increasing bone mineral density. Specific orthopedic expertise is often required to treat fractures in patients with OI. A combination of periodic evaluations, chronic pain control, and disability management is necessary to improve quality of life.

**Keywords:** Dentinogenesis imperfecta. Fractures. Hearing loss. Respiratory failure. Bisphosphonates.

## 1-Introduction

Osteogenesis imperfecta (OI) is the most common genetic bone disease. Its prevalence is of  $1/10^4$  births. Bone fragility with deformities is the hallmark of OI but varies widely in severity. Patients may also exhibit extraosseous manifestations including dentinogenesis imperfecta, blue sclera, joint hypermobility, and/or vascular fragility. The classification developed by Sillence et al. [1] then revised by Warman et al. in 2011 [2] uses clinical criteria to distinguish five types of OI (Table 1). Type 2 OI is rapidly fatal and therefore not seen in adults. OI is caused by monoallelic mutations in the type I collagen genes, which are transmitted on an autosomal dominant basis in 90% of cases. The remaining 10% of patients have recessive forms due to biallelic mutations, usually on autosomes, in genes encoding proteins involved in type I collagen metabolism or in osteoblastogenesis. Type 5, which is characterized by hypertrophic calluses, is due to a mutation in a single gene, *IFITM5*. To date, 18 genes in which mutations may cause OI have been identified, but the list continues to grow [3]. Overlap phenotypes combining bone fragility and abnormalities in other tissues have been reported.

Unexplained bone fragility in an adult who is too young to have postmenopausal or age-related osteoporosis suggests a range of diagnoses including secondary causes of osteoporosis; OI; and other genetic conditions such as Gaucher disease, Marfan syndrome, hypophosphatasia, and syndromes responsible for hypogonadism [4]. Adults in whom previously undiagnosed OI is suspected, and their relatives, must be directed toward a referral center or specific competency center for constitutional bone diseases for a diagnostic evaluation followed by the appropriate management. In France, for example, healthcare professionals involved in managing adults with rare bone, calcium, and cartilage diseases are now linked in a nationwide network known as OSCAR (<https://www.filiere-oscar.fr/>). Oscar

coordinated the publication in 2017 of a national management protocol for OI [5], whose recommendations for adults are summarised in Table 2.

Patients who turn 18 after being diagnosed with OI in childhood are invited to a formal pediatric-to-adult transition meeting with both their former and their future physicians, to ease their passage from one healthcare model to the other and avoid feelings of abandonment. Regular multidisciplinary follow-up is essential and must include periodic evaluations, not only of the bone abnormalities, but also of the multiple extraosseous manifestations that impair function and quality of life [6].

## 2-Extraosseous manifestations

### 2-1 Hearing

Among adults with OI, 22% to 58% have hearing loss, which sets in gradually, usually on both sides. Hearing loss is usually first detected between 15 and 40 years of age and may be conductive, sensorineural, or mixed. The management depends on the type and severity of the hearing loss. Cochlear implants or hearing aids may be required. Stapedectomy corrects conductive hearing loss if performed sufficiently early, and the progression of hearing loss must therefore be monitored closely over time. Surgery, if indicated, carries an increased risk of bleeding and should therefore be performed by a team experienced in treating patients with OI [7].

### 2-2 Respiratory dysfunction

Respiratory dysfunction is a major source of functional impairment, morbidity, and mortality in adults with severe OI. The main causative factors are scoliosis with curvatures exceeding 60° and ribcage deformities, which impair respiratory muscle function and contribute to promote lower respiratory tract infections. A survey of 92 adults with OI

showed a 67% prevalence of vertebral deformities, usually at the thoracic spine, and a 46% prevalence of scoliosis, which was consistently more severe in patients with type 3 compared to type 1 OI. When interpreting lung function test results, the spirometry data must be corrected for arm span, as opposed to height. Severe scoliosis ( $>50^\circ$ ) should be corrected surgically during adolescence to avoid subsequent respiratory failure. Polysomnography to detect sleep apnea syndrome should be obtained in patients with severe OI, cervical spine abnormalities, and/or suggestive clinical symptoms. Finally, the appropriateness of influenza [8] and pneumococcal immunizations should be considered.

### 2-3 Teeth

Dentinogenesis imperfecta has been reported in 5% to 36% of adults with OI and severely affects the permanent teeth, notably the incisors and molars. Discoloration, accelerated decay, and fractures may develop. No correlation in severity exists between the dental and bone abnormalities. Management should be provided at, or in collaboration with, a specific competency center. France has three referral centers for the odontological manifestations of rare diseases, two in Paris (Necker Hospital, coordinator Prof. MP VAZQUEZ; and Rothschild Hospital, coordinator Prof. A BERDAL) and one in Strasbourg (Strasbourg university hospital, coordinator Prof. MC MANIERE).

### 2-4 Bruising and bleeding

Bruising is common, due to increased skin and capillary wall fragility. Primary hemostasis disorders have been reported and, although their pathogenesis is unclear, may involve abnormalities in platelet aggregation when activated platelets contact the extracellular matrix. Surgeons with experience in managing patients with OI frequently report profuse intraoperative bleeding, and several cases of fatal bleeding during surgery or due to a fracture have been described. The bleeding risk is challenging to evaluate, as

standard clotting tests and the bleeding time are normal. Desmopressin therapy, alone or with the antifibrinolytic agent tranexamic acid, has been suggested to minimize the bleeding risk [9].

#### 2-5 Ocular abnormalities

Patients with type 1 or 3 OI often have blue sclera (Table 1). This sign is due to the choroid being visible through the abnormally thin sclera. The cornea may be abnormally thin and fragile, increasing the risk of glaucoma and subsequent optic nerve damage.

Astigmatism, keratoconus, and hydrops (acute traumatic rupture of the corneal Descemet membrane) have also been reported. Refractive disorders should be corrected by glasses, as refractive surgery is contraindicated. Patients should be advised not to rub their eyes and to wear protective goggles during sporting activities.

#### 2-6 Cardiac involvement

In a prospective study, compared to 3435 controls, a population of 687 patients with OI had increased prevalences of mitral and aortic valve incompetence, heart failure, and atrial fibrillation. Dissection and vascular aneurysms were only slightly more common in the patients. The cardiac complications start to occur after 40 years of age. The complex pathophysiology of heart failure in OI involves hypertension facilitated by regular nonsteroidal antiinflammatory drug therapy; as well as physical inactivity and overweight, which may be related to multiple fractures in childhood and/or to fear of fractures in adulthood [10].

#### 3-Pregnancy

Ages at menarche and menopause are similar in patients with and without OI. Both males and females with OI should be informed about antenatal diagnosis procedures before they try to conceive. If the mutation has been identified, the parents can opt for antenatal genetic testing. Among pregnant women with OI, 55% deliver by cesarean section. Maternal complications during pregnancy and delivery occur in about 30% of cases and include worsening of the chronic pain, prepartum bleeding, and preeclampsia. Mothers with OI have a 2-fold increase in the risk of excessive bleeding during delivery, whereas fractures occur in fewer than 2% of cases. Delivery occurs prematurely in 50% of cases [11]. A few anecdotal case reports describe women who received prolonged bisphosphonate therapy during the year preceding conception (or in some cases after conception), with no skeletal abnormalities (other than inherited OI) or growth disorders in the offspring. A single case of transient hypocalcemia has been reported in a breastfed baby of a mother treated with bisphosphonates before conception [12]. Prolonged breastfeeding is not recommended.

#### 4-Musculoskeletal abnormalities

##### 4-1 The craniovertebral junction

Craniovertebral junction abnormalities, usually seen in types 3 and 4 OI, are more common in patients whose height Z score is  $<-3$ . Their prevalence in adults is estimated at 25%. They include platybasia (flattening of the skull base defined as a skull-base angle  $>135^\circ$ ), basilar invagination, and basilar impression. The diagnosis rests on the measurement of several parameters on a lateral skull radiograph, including the position of the dens relative to the foramen magnum. Computed tomography provides an assessment of the bony abnormalities and complementary magnetic resonance imaging determines the degree of involvement of the nervous structures. Basilar impression is the most severe complication



and carries a risk of hydrocephalus and brainstem compression. Warning signs include recurrent headaches, vertigo, torticollis, and alterations in the deep tendon reflexes. The diagnosis must be made before the development of severe signs such as swallowing impairment, paralysis, and malaise, which indicate a risk of sudden death. Bisphosphonate therapy has no effect on basilar impression, which requires surgery. In a prospective longitudinal study of 76 patients with type 1, 3, or 4 OI (including a patient with 40 years' follow-up) [13], craniovertebral junction abnormalities were found in 37% of cases (for all types pooled) and consisted in basilar invagination, platybasia, and basilar impression. Importantly, these abnormalities did not progress with advancing age.

#### 4-2 Tendons and ligaments

Rupture of the Achilles or patellar tendon has been described in numerous anecdotal case-reports. Adults may experience insertional tendinopathy, which may be long-lasting or recurrent, causing functional impairments that may overshadow those due to the fractures [14]. Similarly, some patients have joint hypermobility with instability requiring the use of devices designed for Ehlers-Danlos syndrome sufferers.

#### 4-3 Bone abnormalities

##### 4-3-1 Fractures

The incidence rate of fractures over an 18-year period was evaluated in Denmark in 644 patients with OI and 3361 controls [15]. The fracture incidence rate was higher in the patients than in the controls in all age groups. It decreased from 234/1000 person-years in childhood to 84/1000 person-years between 20 and 40 years of age before rising again, to

112/1000 person-years overall, but with a larger increase in females. The upper-limb long bones and the pelvis were the main fracture sites.

#### 4-3-2 Bone mineral density (BMD) measurement

BMD measured by dual-energy X-ray absorptiometry (DXA) may be low or only minimally diminished in adults with OI. As BMD is an areal measurement, the slenderness of the bones in OI patients may affect the results. In a recent study, BMD at the spine and total hip was comparable in type 1 and types 3/4, whereas femoral neck BMD was lower in types 3/4. Osteoporosis medications provide nearly identical BMD gains to those seen in patients with osteoporosis (see below).

#### 4-3-3 Treatments

##### *4-3-3-1 Orthopedic management*

Orthopedic surgery often requires specific expertise in OI [16]. The slender fragile bones cannot tolerate some types of internal fixation and are at increased risk for intraoperative fracture. Preexisting fixation material may complicate the surgical procedure. Other specific problems are the risk of intraoperative bleeding and of postoperative respiratory failure. Endotracheal intubation requires special precautions in patients with craniovertebral junction abnormalities. A high risk of nonunion of up to 24% after fracture repair and 52% after osteotomy has been reported. As with children, regardless of the type of fracture, early mobilization of the nonimmobilized segments of the fractured limb is recommended.

##### *4-3-3-2 Percutaneous vertebroplasty*

A few anecdotal case-reports of percutaneous vertebroplasty in patients with type 1 have been reported. Pulmonary embolus or hypotension during the cement injection occurred in some patients, although whether these complications were more common than in patients

without OI is unknown. In 1 patient with OI, kyphoplasty 5 months after a lumbar spine fracture provided pain relief [17].

#### *4-3-3-3 Pharmacological treatments of bone fragility*

With all these treatments, appropriate vitamin D and calcium supplements should be provided also.

#### Bisphosphonates

The few clinical studies of bisphosphonates in adults with OI had insufficient statistical power to assess effects in preventing fractures. The inclusion in these studies of patients with varying disease severity probably contributes to the differences in the results.

In Italy, intravenous neridronate every 3 months is recommended in adults with OI. A randomized placebo-controlled double-blind clinical trial was conducted in 46 adults with any type of OI. Mean age was 35 years (range, 21-50 years). After 1 year, the placebo patients were switched to neridronate. Neridronate therapy significantly decreased the levels of bone turnover markers (serum CTX and bone alkaline phosphatase) compared to the placebo and increased the BMD values at the spine and hip by about 8% after 18 months compared to baseline [18]. Another study included 114 patients given intravenous neridronate for 3 years [19]. The findings were similar, with a 9% increase in BMD values. Risedronate 35 mg/week for 2 years was tested in 27 adults with type 1 OI and a mean age of 39 years [20]. BMD increased by 3.9% at the spine but remained unchanged at the hip. The procollagen type 1 N-terminal propeptide (P1NP) decreased by 37%, whereas bone alkaline phosphatase was not affected. The fracture risk remained high, with 25 clinical fractures in 14 patients during the study. Alendronate was evaluated in a 3-year randomized placebo-controlled double-blind trial in 64 patients with any type of OI [21]. Mean BMD gains at the spine were  $10.1\% \pm 9.8\%$  with alendronate and  $0.7\% \pm 5.7\%$  with the placebo.

Serum CTX levels fell by about 80% versus baseline after 1 year in the alendronate group. The fracture risk was unchanged. An observational study of 90 patients compared outcomes with intravenous pamidronate (1.5 mg/kg to 60 mg/infusion over 4 h every 3-4 months, n=28), alendronate (n=10), risedronate (n=17), and no treatment (n=35) over 52 months [22]. Separate results were reported according to the type of OI (1 or 3/4). In the patients with type 1 OI, all the bisphosphonates increased the BMD values at the spine and hip. In contrast, in patients with type 3/4 disease, only pamidronate produced significant BMD gains, and these occurred only at the spine. The incidence of fractures over a 5-year period was unchanged.

Atypical fractures during bisphosphonate therapy have been reported in adults with OI [23], including a case successfully treated with teriparatide [24]. Bisphosphonate-related jaw osteonecrosis has not been described. Mandibular fracture during tooth extractions is known to have occurred in 2 patients with OI. Delayed fracture healing during pamidronate therapy has been reported in children, but not adults, with OI. A Cochrane database systematic review [25] and a metaanalysis [26] showed that all bisphosphonates increased BMD values to a similar extent in patients with OI. However, no proof of efficacy in preventing fractures exists to date. Furthermore, many of the available studies failed to assess quality of life and functional impairment [25].

### Teriparatide

Teriparatide or a placebo was given for 18 months to adults with OI [27]. Of the 40 teriparatide-treated patients, the lumbar spine and femoral BMD values increased significantly, by 6.1% and 2.6%, respectively; whereas the changes in the 39 placebo patients were 2.8% and -2.4%. Serum P1NP and urinary N-telopeptide excretion increased by 135% and 64%, respectively, with teriparatide therapy. Vertebral mechanical strength as assessed by high-resolution peripheral quantitative CT increased by about 15%. Both the

bone turnover marker and the BMD responses were stronger in type 1 than in types 3/4 OI. The incidence of fractures was similar in the teriparatide and placebo groups [27]. In another study, 13 females with type 1 OI who experienced further fractures after several years of neridronate therapy were given teriparatide for 18 months [28]. BMD values increased only at the spine, and increases were seen in the levels of both bone formation and bone resorption markers.

#### Anti-sclerostin antibodies

The anti-sclerostin antibody setrusumab was tested in a 21-week open-label study in patients with moderately severe OI. All the bone formation markers studied increased by more than 50%, and the serum CTX level fell by 44%. BMD values increased by 4% at the lumbar spine [29].

#### Denosumab

Denosumab was used for 24 months in 2 females with OI, both 40 years of age. The safety profile was good, with no hypocalcemia. BMD values increased by about 15% at the spine and hip [30]

### 5-Other treatments

#### *5-1 Non-pharmacological treatments*

Physiotherapy and rehabilitation therapy are recognized as indispensable components of the management of OI. Standardization of these treatments in children is improving, notably after fractures. In contrast, no specific recommendations are available for adults. Physiotherapy is advisable in all patients with symptomatic OI, to prevent further loss of

bone strength due to immobilization of fracture sites and to kinesiophobia. Overall muscle strengthening is in order. In severe forms of OI, attention should be directed to maintaining optimal locomotion and respiratory function. Thus, the physiotherapy program should be tailored to the severity of the disease and functional impairments in each individual patient.

### *5-2 Treatments for chronic pain*

Chronic pain is a major symptom in adults with OI [6,31]. Neither the prevalence nor the severity of the pain correlate with the occurrence of fractures or the severity of the OI. A recent survey conducted by a French patient organization (*Association de l'Ostéogénèse Imparfait*) among adults with OI found that chronic pain impaired quality of life and received insufficient attention from healthcare professionals. Multidisciplinary management of chronic pain should therefore be offered, after a thorough diagnostic evaluation to identify the best analgesic strategies. Pain should be reevaluated periodically and treated throughout follow-up.

### Conclusion

The management of OI in adults is multidisciplinary. The bone abnormalities should be assessed regularly and treatments for bone fragility made available. Although fractures are less common in adults than during childhood, the fracture risk increases again after 40 years of age. The currently available medications have not been proven to diminish the fracture risk but consistently produce BMD gains. The treatment of fractures in patients with OI often requires specific orthopedic expertise. Hearing must be tested periodically, as nearly half the patients experience hearing loss after 40 years of age. Regular monitoring should be provided of the respiratory, ocular, dental, and cardiac manifestations, as

appropriate for the severity of each. Chronic pain should be assessed regularly and treated.

Finally, functional impairments should be appropriately managed.

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**Table 1:** Modified Sillence classification (PNDS, HAS 2017, [1-3]) and modalities of transmission of osteogenesis imperfecta

| Formes d'ostéogénèse imparfaite        |   |  |                           |                     |
|--|---|--|---------------------------|---------------------|
| Type                                   | Severity  | Phenotype  | Dentinogenesis imperfecta | Inheritance         |
| 1                                      | Moderate (no deformities)                             | Moderate number of fractures; height normal or slightly decreased; blue sclera   | Inconsistently present    | AD or X-linked      |
| 2                                      | <i>Fatal during the perinatal period</i>              | <i>Multiple fractures, severe deformities, short stature</i>   |                           |                     |
| 3                                      | Severe and/or responsible for progressive deformities | Multiple fractures, short stature, sclera ± gray, triangular face, deformities, scoliosis                              | Present                   | AD, AR, or X-linked |
| 4                                      | Intermediate with short stature                       | Variable fractures including vertebral fractures, moderate scoliosis, normal sclera                                    | Present                   | AD, AR, or X-linked |
| 5                                      | Variable, with hypertrophic calluses                  | Variable stature, hypertrophic calluses, radial head dislocation and interosseous membrane ossification, normal sclera | Absent                    | AD                  |
| Overlap and/or associated phenotypes   |   |  |                           |                     |
| X-linked osteoporosis                  |   |  |                           | X-linked            |
| Primary osteoporosis (+/- familial)    |   |  |                           | AD                  |
| Idiopathic juvenile osteoporosis       |   |  |                           | Sporadic            |
| Bruck syndrome                         |   |  |                           | AR                  |
| Osteoporosis-pseudoglioma syndrome     |   |  |                           | AR                  |
| Cole-Carpenter syndrome                |   |  |                           | AD                  |
| Spondylo-ocular syndrome               |   |  |                           | AD                  |
| Ehlers-Danlos syndrome, progeroid type |   |  |                           | AR                  |
| Geroderma osteodysplastica             |   |  |                           | AR                  |
| Hajdu-Cheney syndrome                  |   |  |                           | AD                  |

AD, autosomal dominant; AR, autosomal recessive

Table 2: Recommendations for managing osteogenesis imperfecta in adults (PNDS 2017, HAS )

| <b>Moderately severe OI</b>                      |                                   |   |                                     |
|--|-----------------------------------|---|-------------------------------------|
| <i>Providers and minimal follow-up intervals</i> | <i>Clinical symptoms</i>          | <i>Investigations</i>   | <i>Management</i>                   |
| Rheumatologist and Orthopedic surgeon (3 years)  | Pain                              | EOS and MRI of CVJ if needed  | Vitamin D, dairy products           |
| Rehabilitation therapist (as needed)             | Moderate linear growth deficiency | BMD if ↑ in fractures   | Analgesics, Antiinflammatory agents |
| ENT specialist (5 years)                         | Dental complications              | Calcium and phosphate levels  | Career support                      |
| Dentist (yearly)                                 | Hearing impairment                | Audiometry every 5 years  | Physical activities, physiotherapy  |
| Specialized obstetrician if pregnancy            | Psychological difficulties        | Echocardiography every 10 years                                     | Genetic counseling                  |
|  | Excess weight                     |   | Psychological support               |
|  |                                   |   | Support during pregnancy            |
| <b>Complicated and/or severe OI</b>              |                                   |   |                                     |
| <i>Providers and minimal follow-up intervals</i> | <i>Clinical symptoms</i>          | <i>Investigations</i>   | <i>Management</i>                   |
| Rheumatologist (3 years)                         | Pain                              | X-rays as needed  | Vitamin D, dairy products           |
| Orthopedic surgeon (3 years)                     | Variable linear growth deficiency | BMD if ↑ in fractures   | Analgesics, Antiinflammatory agents |
| Physical medicine and rehabilitation specialist  | Dental complications              | Calcium and phosphate levels  | Career support                      |
| ENT (5 years)                                    | Hearing impairment                | Lung function tests and polysomnography every 1-2 years if abnormal | Bone turnover modulators            |
| Dentist (yearly)                                 | Psychological difficulties        |   | Physical activities, physiotherapy  |
| Pulmonologist (3 years)                          | Excess weight                     | Audiometry every 5 years  | Genetic counseling                  |
| Specialized obstetrician if pregnancy            |                                   | Echocardiography every 5-10 years                                   | Psychological support               |
|  |                                   |   | Support during pregnancy            |

MRI, magnetic resonance imaging; CVJ, craniovertebral junction; BMD, bone mineral density