Osteogenesis imperfecta: from diagnosis and multidisciplinary treatment to future perspectives

Aline Bregou Bourgeois, Bérengère Aubry-Rozier, Luisa Bonafè, Lee Ann Applegate, Dominique P. Pioletti, Pierre-Yves Zambelli

Summary

Osteogenesis imperfecta is an inherited connective tissue disorder with wide phenotypic and molecular heterogeneity. A common issue associated with the molecular abnormality is a disturbance in bone matrix synthesis and homeostasis inducing bone fragility. In very early life, this can lead to multiple fractures and progressive bone deformities, including long bone bowing and scoliosis. Multidisciplinary management improves quality of life for patients with osteogenesis imperfecta. It consists of physical therapy, medical treatment and orthopaedic surgery as necessary. Medical treatment consists of bone-remodelling drug therapy. Bisphosphonates are widely used in the treatment of moderate to severe osteogenesis imperfecta, from infancy to adulthood. Other more recent drug therapies include teriparatide and denosumab. All these therapies target the symptoms and have effects on the mechanical properties of bone due to modification of bone remodelling, therefore influencing skeletal outcome and orthopaedic surgery. Innovative therapies, such as progenitor and mesenchymal stem cell transplantation, targeting the specific altered pathway rather than the symptoms, are in the process of development.

Key words: osteogenesis imperfecta; bisphosphonates; mesenchymal stem cell; telescopic rods

Introduction

Osteogenesis imperfecta (OI), commonly referred to as brittle bone disease, is a rare genetic disease with an incidence of 1/15 000–20 000. In 1979, Sillence et al. published the first description of four OI groups (OI I–IV) (table 1) with specific genetic inheritance, based on specific phenotypes (clinical, radiographic and pedigree features) [1]. In 1983, Chu et al. reported the presence of an internal deletion in a collagen gene (COL1A1) [2] implicated in OI. Altogether, several autosomal mutations in the COL1A1 and COL1A2 genes, coding for the alpha-1 and alpha-2 chains of collagen type I, were discovered in the four OI groups known at that time. In 2004, Glorieux and Rauch described three new OI groups, with specific clinical characteristics and without genetic modification in COL1A1 or COL1A2 (OI V–VII) [3]. Barnes et al. described the first non-COL1A1/2 autosomal recessive mutation in 2006 [4]. Since this time, multiple new genes implicated in collagen expression, structure and function have been discovered, elaborating a more extensive genetic classification. The majority of OI patients have autosomal dominant mutations affecting type I collagen genes (COL1A1, COL1A2), resulting in reduced production or abnormal type I collagen formation and thus leading to bone fragility (fig. 1). Rare autosomal recessive or X-linked mutations (6–8% of all OI cases) have been identified, involving procollagen modifications, collagen fibre maturation, and bone formation and mineralisation [5]. In the 2015 revision of the nosology and classification of genetic skeletal disorders, the Sillence classification based on phenotype is still used [6], since the diagnosis, classification and severity assessment of OI is based on the clinical phenotype over time [7].

Classification

Since the Sillence description of four OI types (OI I–IV), more than 1500 dominant mutations in COL1A1/2 genes have been identified. These mutations alter the structure or the quantity of collagen type I and lead to skeletal phenotypes ranging from subclinical to lethal OI [8]. Recessive mutations in collagen-related genes, where the related proteins interact with type I collagen, cause lethal to moderate OI phenotypes. It became, therefore, impossible to maintain a close correlation between the molecular genetic basis and the Sillence OI types. In 2010, the Nosology Group of International Skeletal Dysplasia Society decided to use the Sillence classification as the prototypic and universal way to classify the degree of severity in OI (INCDs classification). They separated the Sillence classification from molecular reference, and listed separately many genes in-
volved in OI [9]. At this time, arabic numbers instead of roman numerals were used for types of OI, to emphasise the phenotypic aspect, since roman numbers have been used to classify new genetic mutations [7]. In 2015, the revised INCDS classification was still associated with the Sillence classification, being phenotypically rather than molecularly based. OI type 5 was introduced into the classification as it is radiologically phenotypically distinguishable from types 1–4.

Therefore, despite the multiplicity of new genes discovered in the field of OI, genetic classification (table 2) is not currently used in clinical practice, and the phenotype classification is still the rule (table 3) [6]. Concomitantly with the new INCDS OI classification, universal criteria to classify the degree of severity of OI were needed. Van Dijk and Sillence proposed a severity grading scale (table 4) [7]. This relies on clinical and historical data, overall skeletal condition with fracture timing (prenatal/prepubertal) and frequency, bone densitometry, mobility and ambulatory level. It allows comprehension of the course of the disease for patients, highlights the treatment possibilities (surgical, pharmacological and conservative) and helps the physician to evaluate therapy. The grade of severity of the disease is based on phenotype observations and OI is clinically graded from mild to extremely severe (table 4). This scale has been already used in a multicentre study [10]. Possible treatment has been included by the scale authors. The scale is still under validation in specialised centres, but importantly gives a wide overview of the OI severity spectrum.

Table 1: 1979 Sillence classification of osteogenesis imperfecta.

<table>
<thead>
<tr>
<th>OI Type</th>
<th>Inheritance</th>
<th>Features</th>
</tr>
</thead>
</table>
| I       | AD          | Osseous fragility (variable)  
Adulthood hearing loss  
Blue sclerae |
| II      | AD, AR      | Extremely severe osseous fragility  
Perinatally lethal |
| III     | AR          | Moderate to severe osseous fragility  
Normal sclerae  
Severe deformity of long bones and spine  
Variable clinical and radiographic phenotypes |
| IV      | AD, AR      | Osseous fragility  
Generally normal sclerae  
Severe deformity of long bones and spine |

AD = autosomal dominant; AR = autosomal recessive; OI = osteogenesis imperfecta

Table 2: Genetic and molecular classification of osteogenesis imperfecta.

<table>
<thead>
<tr>
<th>Molecular pathway</th>
<th>Gene</th>
<th>Heredity</th>
<th>Silence phenotype</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen I structural defect or haploinsufficiency</td>
<td>COL1A1</td>
<td>AD</td>
<td>I, II, III, IV</td>
<td>Blue/grey/normal sclerae</td>
</tr>
</tbody>
</table>
| Collagen I structural defect or haploinsufficiency | COL1A2  | AD       | I, II, III, IV    | Hyperlaxity  
Hypoacusia  
Dentinogenesis imperfecta |
| Prolyl-3-hydroxylase complex         | ORTAP   | AR       | II, III, IV (VII) |           |
|                                    | LEPREI  | AR       | II, III (VIII)    |           |
|                                    | PPIB    | AR       | II, III, IV (IX)  | Pterygium |
|                                    | PLOD2   | AR       | III              | Congenital articular contractures (Bruck syndrome type 2) |
| Lysyl-hydroxylase telopeptide       | FKBP10  | AR       | III, IV (XI)     | Eventual congenital articular contracture (Bruck syndrome type 1) |
|                                    | SERPINH1| AAR      | II, III (X)      | Blue sclerae  
Dentinogenesis imperfecta |
| Collagen chaperone                  | BMP1    | AR       | XIII             | Elevated bone density  
Blue sclerae |
| Osseous homeostasis and formation, bone mass regulation | SERPINF1| AR       | III, IV (VI)     | Progressive low bone mass  
Poor response to bisphosphonates  
Good response to anti-RANKL antibody |
|                                    | SP7     | AR       | III (XII)        | Delayed dental eruption |
|                                    | LRP5    | AR       | III, IV          | Visual impairment (osteoporosis-pseudoglioma syndrome) |
|                                    | WNT1    | AR       | III, IV (XV)    | Progressive evolution  
Poor response to bisphosphonates |
|                                    | TMEM38B | AR       | III (XIV)        |           |
|                                    | CREB3L1 | AR       | II, III          |           |

AD = autosomal dominant; AR = autosomal recessive; OI = osteogenesis imperfecta; RANKL = receptor activator of nuclear factor-κB ligand

Roman numbers are used for Sillence types as this concerns the genetic classification (cf text)
Clinical findings

OI diagnosis is based on clinical and radiographic findings. OI types 1, 4 and 5 are phenotypes with mild to moderate severity, while OI types 2 and 3 are severe to extremely severe phenotypes. OI type 1 is the non-deforming form with blue sclerae (fig. 2). OI type 4 is a common variable form with normal sclerae; OI type 5 is a form with interosseous membrane calcification. OI type 3 is a severe, progressively deforming form and OI type 2 is an extremely severe, perinatally lethal form.

Clinical features are directly linked to the fact that OI is a generalised, predominantly collagen-tissue disorder. Depending of the causative mutation, the primary structural defect of type I collagen, insufficient collagen quantity, and the posttranslational modification, folding, intracellular transport or matrix incorporation of abnormal colla-
are uncommon and NAI cannot be ruled out in favour of OI [16].

**Clinical management**

Amelioration of mobility, self-care, functional independen-
tce and better quality of life at an adult age are the main
goals of the proposed therapeutic approaches. These treat-
ment plans are based on a multidisciplinary approach,
which includes medical management of bone-remodelling
drug therapy; orthopaedic treatment (conservative or sur-
gical) for fractures and deformity stabilisation; rehabili-
tation for muscular strengthening and movement or a walk-
ing strategy. The multidisciplinary approach has led to bet-
ter functional outcomes for patients but its practical ap-
lication depends nevertheless on the degree of OI severity
[17–19].

As shown in table 3, prognosis and management are
strongly related to the type of OI. It is noteworthy that
severity is highly variable even within OI families, and
treatment is guided by the severity rather than the type of
OI. In mild non-deforming OI, diagnosis is usually accom-
plished during childhood or early puberty, when fractures
for minor trauma or bone pain in association with low bone
mineral density occur. These patients rarely develop long
bone deformities. Surgery is rarely necessary and is more
dependent on the fracture type than the disease itself. Frac-
ture healing is normal in OI, and if no internal fixation
is needed, cast immobilisation duration is the same as for
healthy children. Casts should not be maintained more than
necessary and mobilisation should be as soon as possible
to minimise secondary bone fragility and mobility diminu-
tion.

In moderate or severe OI, very early fractures and/or bone
deformities occur. Early correction of long bone deform-
tities and bone fragility stabilisation with intramedullary
rodding has been associated with better motor status im-
provement and ambulation in severe OI [20, 21]. Plates
are contraindicated as all the stress could be transferred
to the plate and thus the underlying bone would become
less strong, with subsequent fractures at the plate extremiti-
ties. Telescopic growing rods can be used and have been
associated with a lower rate of re-rodding [18]. Together
with surgery, moderate and severe forms of OI benefit from
specific drug therapies. Generally, long bone deformations,
vertebral fractures and frequent fractures should raise the
possibility of bisphosphonate treatment. Bisphosphonate
treatment is the most frequently used. Bisphosphonate con-
centrates in the mineralised osseous matrix where it inhi-
bits bone resorption by osteoclasts (fig. 1) and correspon-
dingly favours an increase in bone mineral density.

Prior to starting a bisphosphonate it is essential to maxim-
ise calcium and vitamin D supplementation, as sufficient
concentrations are necessary for an optimal treatment re-
sponse [22]. Bisphosphonate can be administered to chil-
dren younger than 24 months old with net results on de-
creased fractures rates and increased patient mobility [23,
24], but without reversing the fracture rate or scoliosis
evolution of severe OI to a mild OI situation [25]. Studies
have shown a diminished fracture risk for children without
alteration of linear growth [10, 23, 24, 26, 27]. Augmenta-
tion of cortical thickness and vertebral height, and diminu-
tion of musculoskeletal pain and fatigue are described as
results of bisphosphonate treatment [28]. Bisphosphonates
have a half-life in bone of more than a decade, and at the
end of the treatment they still have an impact on bone
modelling and quality [29, 30]. Bisphosphonates do not
delay bone healing after fracture, but it is recommended to
avoid sawing techniques for surgical osteotomies as heat-
ing may alter bone consolidation; there is a generally ac-
cepted consensus to keep an interval of 2–4 months after
surgery free of bisphosphonate infusions [31, 32]. Bisphos-
phonate treatments have, however, raised some concerns
about atypical femoral stress fractures due to suppression
of remodelling and the secondary loss of bone elasticity
on the long bone mechanical stress zone. Awareness about
their benefits and risks, limited duration and a bone me-
chanical axis as physiological as possible seem to be the bet-
ter guarantee against these atypical fracture risks [33–36].

Therefore, although they are commonly used, due to poten-
tial risks, the decision to use bisphosphonate therapies
must be individualised.

Despite the amelioration of bone density and fracture risk,
patients under bisphosphonate treatment still have long
bone fractures and progressive scoliosis, and these are still
of concern, even in mild forms of OI [37]. Scoliosis is the
second major orthopaedic concern in OI, with a prevalence
ranging from 39% to 88% [38]. In mild OI the majority are
self-limited, but in moderate to severe OI evolution can be
severe, even with bisphosphonate treatment. This leads to
the hypothesis that, although deformity from repetitive ve-
tebral fractures, and altered bone quantity and quality are
commonly reported as contributory factors, ligament lax-
ting and muscle weakness are also important factors in the
pathophysiology of scoliosis in OI [39]. Bracing is ineffec-
tive and contraindicated because of secondary chest and
rib deformities [40, 41]. Arthrodesis with posterior spinal
instrumentation is needed for a progressive curve reaching
50° to stop curve progression and prevent pulmonary
impairment; types 3 and 4 OI are mainly concerned. The
arthrodesis may be preceded by a period of cranial halo
traction for very severe curves [42]. Other spinal deform-
ties such as thoracolumbar kyphosis, lumbosacral spon-
dylolisthesis, and basilar invagination at the craniovertebral
junction are frequently seen and may necessitate interven-
tions [40].

In severe OI, upper limb long bone deformities with severe
bowing and radial head dislocation are frequent and very
disabling. Surgical correction is indicated in order to re-
lieve pain if present, and when functional abilities are af-
fected (self-care, wheelchair autonomous hand-rolling)
[43, 44]. Pelvic and hip progressive deformations occur in
severe OI: coxa vara has a very negative effect on the
functional status of the patient and hip correction inter-
ventions may be necessary [45, 46]; severe acetabular pro-
trusion induces hip stiffness and can have some urinary or
gastrointestinal tract implications that, however, rarely
need intervention. Report of one case requiring colostomy,
femoral traction and pelvic osteotomy to release intestinal
compression does exist [47, 48].

Besides drug therapy and orthopaedic management,
physiotherapy is key in OI management. For many years,
rehabilitation programmes have been proposed for OI patients and have gained in efficacy since the introduction of bisphosphonates into OI management [49]. In children, gross motor development acquisition, safety in active movement and minimisation of the development of early complications are the predominant targets. Rehabilitation strategies are individualised depending on clinical assessment and function [50]. OI type and total muscle strength being strongly associated with ambulation, particular attention to muscle training and maintenance is warranted [51, 52]. Indeed, regular physical activity is important in OI management. The type of activity is directly linked to the type of OI. Compared with healthy children, OI type 1 children have muscle weakness independent of a hypoactive activity level [52–54].

**Recent medical treatment options**

Despite the use of bisphosphonates, several potential interesting alternatives could be used in the drug therapy for OI. Teriparatide (derived from recombinant human parathyroid hormone) has been shown to stimulate bone formation and has a beneficial effect on bone mineral density, but has no impact on the fracture risk in this population (insufficient data). There is some evidence that teriparatide could ameliorate healing of atypical femoral stress fracture in adults [33], but no evaluation has been reported of teriparatide use in children with OI and there is concern about a neoplastic risk in children [55, 56].

Denosumab (an anti-RANK [receptor activator of nuclear factor-κB] ligand antibody) inhibits osteoclast formation and bone resorption. It has been approved during the last decade for the treatment for osteoporosis in postmenopausal women and recently for men [57]. In children, 2-year periods of treatment in four OI type VI patients have been reported. OI type VI bone is characterised by an increased amount of non-mineralised osteoid. Bisphosphonate binds to mineralised bone surface and lack of bisphosphonate binding is thought to be one of the reasons for a low response to bisphosphonate treatment in OI type VI. During the treatment period no severe side effects were noticed but slight hypocalcaemia suggested that calcium supplementation should be given. Denosumab is degraded within 3–4 months and has no long-term accumulation such as bisphosphonates have. During the observed period, there was no impact on longitudinal bone growth and denosumab led to an increase of bone mineral density and mobility, and a marked and reversible suppression of bone resorption [58, 59]. However, no long-term data exist in children and further studies are needed to evaluate the long-term safety and benefits.

A new treatment, an antiserclerostin antibody, is in development in osteoporosis and has shown an interesting benefit in OI. Already tested in OI mice, the antiserclerostin antibody is promising through its mechanism of action: it decouples bone formation and resorption in favour of bone formation, with an important gain in bone quantity [60]. Human studies in OI are ongoing.

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<table>
<thead>
<tr>
<th>OI Type</th>
<th>Inheritance</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AD</td>
<td>Non-deforming form Osseous fragility Presenile hearing loss Blue sclera</td>
</tr>
<tr>
<td>2</td>
<td>AD, AR</td>
<td>Perinatal lethal form Extremely severe osseous fragility</td>
</tr>
<tr>
<td>3</td>
<td>AD, AR</td>
<td>Progressively deforming form Moderate to severe osseous fragility</td>
</tr>
<tr>
<td>4</td>
<td>AD, AR</td>
<td>Moderate form Generally normal sclerae</td>
</tr>
<tr>
<td>5</td>
<td>AD, AR</td>
<td>Calcification of the interosseous membrane and/or hypertrophic callus</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; OI = osteogenesis imperfecta

**Table 4:** Pre- and postnatal severity grading scale (adapted from Van Dijk FS, Silence DO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A. 2014;164A:1470–81).

<table>
<thead>
<tr>
<th>Intrauterine (ultrasound at 20 weeks of pregnancy)</th>
<th>Growth velocity and height</th>
<th>Intrinsic bone deformations</th>
<th>Annualised prepubertal # rate</th>
<th>Locomotion status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild OI</td>
<td>No #. No long bone deformities</td>
<td>Normal or near normal</td>
<td>None</td>
<td>≤1</td>
</tr>
<tr>
<td>Moderate OI</td>
<td>Rare fetal long bone # or bowing</td>
<td>Decreased</td>
<td>Anterior femoral and tibial bowing</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Severe OI</td>
<td>Long bones shortening Long bone # and bowing Rib #</td>
<td>Severely decreased</td>
<td>Long bone and spine progressive deformity</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Extremely severe OI</td>
<td>Long bone shortening Long bone # and bowing Rib #</td>
<td>Multiple long bone fractures at birth, all vertebrae are crushed, small thorax, respiratory distress</td>
<td>Perinatally lethal course</td>
<td></td>
</tr>
</tbody>
</table>

# = fracture; OI = osteogenesis imperfecta
Innovative therapies for a cure for osteogenesis imperfecta

The current treatments and new drug therapies proposed for OI target only the symptoms and there is a definite need to develop a solution that could lead to a cure for OI. Progress in genetic or molecular diagnosis have led to a better understanding of the physiopathology of OI, permitting, for example, a specific molecular treatment for OI type VI with denosumab [58, 61], and potentially could open the door to more appropriate treatments, targeting the specific altered pathway [62]. Gene targeting in mesenchymal stem cells from OI individuals has been possible in mice, with resultant normal collagen and bone production in vivo. [63, 64] Gene silencing using small interfering RNAs has been possible in vitro in human bone derived cells. There is still necessity for clinical trials of gene therapy. Preclinical studies using different in-vivo models [65–67] suggest some potential effect with bone marrow transplantation in treating OI and are consistent with clinical transplantation of mesenchymal stem cells or whole bone marrow in children with severe forms of OI. The first clinical trial involved the treatment of children suffering from OI with allogeneic bone marrow-derived mesenchymal cells from HLA-identical or single-antigen-mismatched siblings. An increase in bone condition (increase in growth velocity and bone mineral content, reduced frequency of bone fracture) during 6 months following the infusion was observed [68]. A further study by the same group involving five OI children was performed (again with HLA-compatible donors). It was mentioned that, ideally, therapy for OI should be directed toward improving bone strength by improving the structural integrity of collagen and thereby the quality of the bone. The positive effect of the first study was still observed after 36 months, while a decrease in efficacy compared with the initial 6 months was also observed. The working hypothesis of the study was that bone marrow transplants contain mesenchymal precursor cells that can engraft in the skeleton and generate osteoblasts capable of modifying abnormal bone structure. The cell engraftment in the bone marrow is then a key aspect for a successful and, hopefully, long-lasting treatment of OI with a cell therapy strategy.

As a result of the promising results of the previous clinical trials, a study involving the injection of mesenchymal stem cells obtained from the same donors as those used for bone marrow transplantation was performed. It was found that allogeneic bone marrow-derived mesenchymal cells could engraft in bone, marrow stroma and skin without the requirement for preparative chemotherapy, and then produce clinically measurable benefits. However, it was also suggested that a beneficial effect from transplanted whole marrow might not be available from infusions of isolated donor mesenchymal stem cells. It is proposed that other cell types should be used [69]. An additional study was performed on a single human fetus presenting an OI disorder. Allogeneic fetal mesenchymal stem cells were transplanted in utero, and the cells were shown to engraft and differentiate into bone even when the recipient was immunocompetent and HLA-incompatible. However, very low engraftment (0.3%) could still be demonstrated in bone at 9 months of age [70]. Ideal cell types to be engrafted could include bone marrow, mesenchymal stem cells from bone marrow or adipose tissue, preosteoblasts and fetal bone cells (genetically modified or not). The technical requirements for obtaining and expanding each of these cell types vary considerably and should be taken into consideration. Indeed, if cells can be expanded easily to very large numbers and stored in liquid nitrogen with high survival, the cell source will perhaps be more dependable for implantation. Mesenchymal cells are known for low viability upon engraftment and techniques to assure increased stability of cell sources are imperative. Fetal bone cells have been evaluated for therapeutic use since they can be expanded from one small tissue fragment to develop a clinically dedicated cell bank capable of stockng cells for hundreds of thousands of treatments. These cells have the advantages of a high proliferation rate and early mineralisation and, unlike mesenchymal cells, are already differentiated and dedicated to bone formation without dedifferentiation to other cell types. Overall, they may provide a stable cell source for therapeutic use in the future, potentially in all types of OI [71, 72]. Altogether, the clinical studies to date suggest promising beneficial effects of cell transplantation in OI even if statistical significance of the reported studies was often lacking owing to the small number of patients involved in each study. The delivery methods and cell choice, as well as the question of the role and the side effects of cell chimerism, have to be addressed in order to improve long-lasting effects of cell therapies in OI.

Conclusion

There is currently no completely satisfactory treatment for OI, and any treatments either altering bone resorption or stimulating bone formation have an impact on the mechanical properties of bone. Bisphosphonates are an adjuvant treatment to intramedullary rodding and other surgical procedures, but concern about properties of bone microarchitecture remodelling capacities persists. Bone remodelling with future cell therapies may be promising in OI treatment.

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References


Collagen type I biosynthesis and bone formation. Collagen I is a triple helix with two alpha-1 and one alpha-2 chains encoded by COL1A1 and COL1A2 genes. After translation, the pro-alpha-chains are translocated in the rough endoplasmic reticulum (rER) where posttranslational modifications occur (1)(2). The chains are folded in a triple helix, composed of two alpha-1 and one alpha-2 chains (2). These steps are, among others, under the control of CRTRAP, LEPRE 1, PPIB and FKBP10 genes. The procollagen is then further modified during the transport to the Golgi apparatus (influence of SERPINH1, PLOD2 and FKBP10 genes). The procollagen is then delivered into the extracellular matrix by exocytosis. There, cleavage and removal of the pro-peptides N and C results in collagen I formation (3). Crosslinking of collagen molecules leads to fibril formation. Assembly of multiple collagen type I fibrils leads to collagen fibres which are constituents of bone (4). Osteoblasts produce a collagen-rich extracellular matrix that will be mineralised and osteoclasts degrade bone. Bone formation and resorption is regulated through cross-talk between osteoblasts and osteoclasts. In osteogenesis imperfecta, altered quality and/or quantity of collagen I formation, altered cross-talk between osteoblasts and osteoclasts, leads to a defect in bone formation. Bisphosphonates concentrate in the mineralised osseous matrix where they inhibit bone resorption by osteoclasts.
Figure 2

Characteristics of osteogenesis imperfecta (OI) types 1–5, illustrating morphological features for each stage.