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Osteogenesis imperfecta: from diagnosis and multidisciplinary treatment to future perspectives

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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 involved 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.

OI Type	Inheritance	Features
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.

Molecular pathway	Gene	Heredity	Sillence phenotype	Features
Collagen I structural defect or haploinsufficiency	*COL1A1*	AD	I, II, III, IV	Blue/grey/normal sclerae Hyperlaxity Hypoaccousia Dentinogenesis imperfecta
	COL1A2	AD	I, II, III, IV	
Prolyl-3-hydroxylase complex	*CRTAP*	AR	II, III, IV (VII)	
	LEPREI	AR	II, III (VIII)	
	PPIB	AR	II, III, IV (IX)	
Lysyl-hydroxylase telopeptide	*PLOD2*	AR	III	Pterygium Congenital articular contractures (Bruck syndrome type 2)
Collagen chaperone	*FKBP10*	AR	III, IV (XI)	Eventual congenital articular contracture (Bruck syndrome type 1)
	SERPINH1	AAR	II, III (X)	Blue sclerae Dentinogenesis imperfecta
Collagen type I maturation	*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	
Unknown function	*IFITM5*	AD	V	Hypertrophic callous Interosseous membrane calcifications Sclerotic metaphyseal band
	PLS3	X-linked	I	Early osteoporosis for heterozygous female Type I OI for hemizygous males

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 collagen lead to an abnormal bone matrix and reduced bone strength, with resulting bone fragility, higher fracture risk, bone deformity and linear growth deficiency (fig. 2). Iterative fractures with mild trauma are then observed even at a young age, as well as joint laxity and weak muscle tone. Progressive skeletal deformities including bowing deformities of long bones, scoliosis, kyphosis, basilar impression, and chest wall deformities such as pectus excavatus or carinatus (i.e. barrel chest) are possible. Depending on OI severity, patients present variable degrees of short stature, OI type 1 having none to mild linear growth deficiency, OI type 4 having mild to moderate, and OI type 3 with very severe [11, 12]. Ambulation and mobility is limited in severely affected patients. Radiographic characteristics include osteopenia, bowed long bones, thin and under-tubularised long bones, gracilis ribs, vertebral compression and narrow thoracic apex (fig. 2 radiograph) [13]. Extraskeletal manifestations include blue sclerae, easy bruising owing to cutaneous and vascular fragility, progressive hearing loss in young adulthood, variable progressive impairment of pulmonary function and dentinogenesis imperfecta (fig. 2) [5, 7, 14]. Compared with healthy controls, OI patients seem to have a slightly increased risk of developing cardiac valvular disease, but more studies are needed to support this hypothesis [15]. Differential diagnosis is sometimes difficult between the mild forms of OI and of child abuse in children, or between OI and primary osteoporosis in older patients. Distinction between OI and child abuse (also called nonaccidental injury: NAI) is mainly based on history, clinical examination and radiography. Trauma description should be consistent with the clinical and radiological findings. OI and NAI children may have multiple bruises and contusions, but, despite a tendency for bruising capacity in OI, multiple and unusually localised hematomas are not the rule and should raise the suspicion of NAI. Radiological features of NAI and OI include multiple fractures of various ages, diaphyseal and vertebral fractures, anterior and lateral rib fractures, and hyperplastic callus formation. NAI children do not have osteopenia, long bone or skull deformities. Children with OI do not usually have typical corner metaphyseal lesions, spinous processes or posterior rib fractures. Multiple fractures in a child with OI type 1

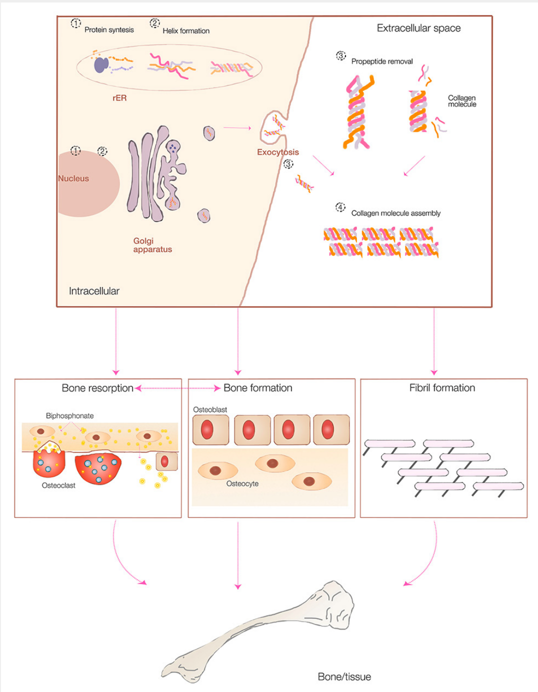

Figure 1

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 *CRTAP*, *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 1 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 osteoblasts, leads to a defect in bone formation. Bisphosphonates concentrate in the mineralised osseous matrix where they inhibit bone resorption by osteoclasts.

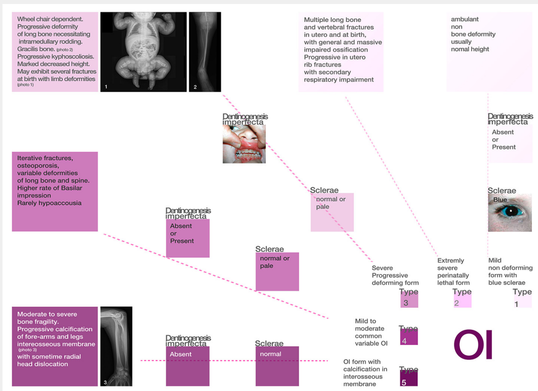

Figure 2

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

are uncommon and NAI cannot be ruled out in favour of OI [16].

Clinical management

Amelioration of mobility, self-care, functional independence and better quality of life at an adult age are the main goals of the proposed therapeutic approaches. These treatment plans are based on a multidisciplinary approach, which includes medical management of bone-remodelling drug therapy; orthopaedic treatment (conservative or surgical) for fractures and deformity stabilisation; rehabilitation for muscular strengthening and movement or a walking strategy. The multidisciplinary approach has led to better functional outcomes for patients but its practical application 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 accomplished 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. Fracture 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 diminution.

In moderate or severe OI, very early fractures and/or bone deformities occur. Early correction of long bone deformities and bone fragility stabilisation with intramedullary rodding has been associated with better motor status improvement 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 extremities. 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 concentrates in the mineralised osseous matrix where it inhibits bone resorption by osteoclasts (fig. 1) and correspondingly favours an increase in bone mineral density. Prior to starting a bisphosphonate it is essential to maximise calcium and vitamin D supplementation, as sufficient concentrations are necessary for an optimal treatment response [22]. Bisphosphonate can be administered to children younger than 24 months old with net results on decreased 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]. Augmentation of cortical thickness and vertebral height, and diminution 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 heating may alter bone consolidation; there is a generally accepted consensus to keep an interval of 2–4 months after surgery free of bisphosphonate infusions [31, 32]. Bisphosphonate 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 mechanical axis as physiological as possible seem to be the better guarantee against these atypical fracture risks [33–36]. Therefore, although they are commonly used, due to potential risks, the decision to use bisphosphonate therapies must still 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 vertebral fractures, and altered bone quantity and quality are commonly reported as contributory factors, ligament laxity and muscle weakness are also important factors in the pathophysiology of scoliosis in OI [39]. Bracing is ineffective 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 deformities such as thoracolombar kyphosis, lumbosacral spondylolisthesis, and basilar invagination at the craniocervical junction are frequently seen and may necessitate interventions [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 relieve pain if present, and when functional abilities are affected (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 interventions may be necessary [45, 46]; severe acetabular protrusion 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 antisclerostin antibody, is in development in osteoporosis and has shown an interesting benefit in OI. Already tested in OI mice, the antisclerostin 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.

Table 3: Current modified phenotypic Sillence classification of osteogenesis imperfecta from the Nosology Group of the International Skeletal Dysplasia Society (adapted from Bonafé L, et al. Nosology and Classification of Genetic Skeletal disorders: 2015 Revision. Am J Med Genet A. 2015;167A(12):2869-92 9999A:1–24).

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

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

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

	Intrauterine (ultrasound at 20 weeks of pregnancy)	Growth velocity and height	Intrinsic bone deformations	Annualised prepubertal # rate	Locomotion status
Mild OI	No #, No long bone deformities	Normal or near normal	None	≤1	Ambulant
Moderate OI	Rare fetal long bone # or bowing	Decreased	Anterior femoral and tibial bowing	>1	Ambulant
Severe OI	Long bones shortening Long bone # and bowing Rib #	Severely decreased	Long bone and spine progressive deformity	>3	Wheel-chair dependent
Extremely severe OI	Long bone shortening Long bone # and bowing Rib # ↓Mineralisation	Multiple long bone fractures at birth, all vertebrae are crushed, small thorax, respiratory distress Perinatally lethal course			

= 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 stocking 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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Figures (large format)

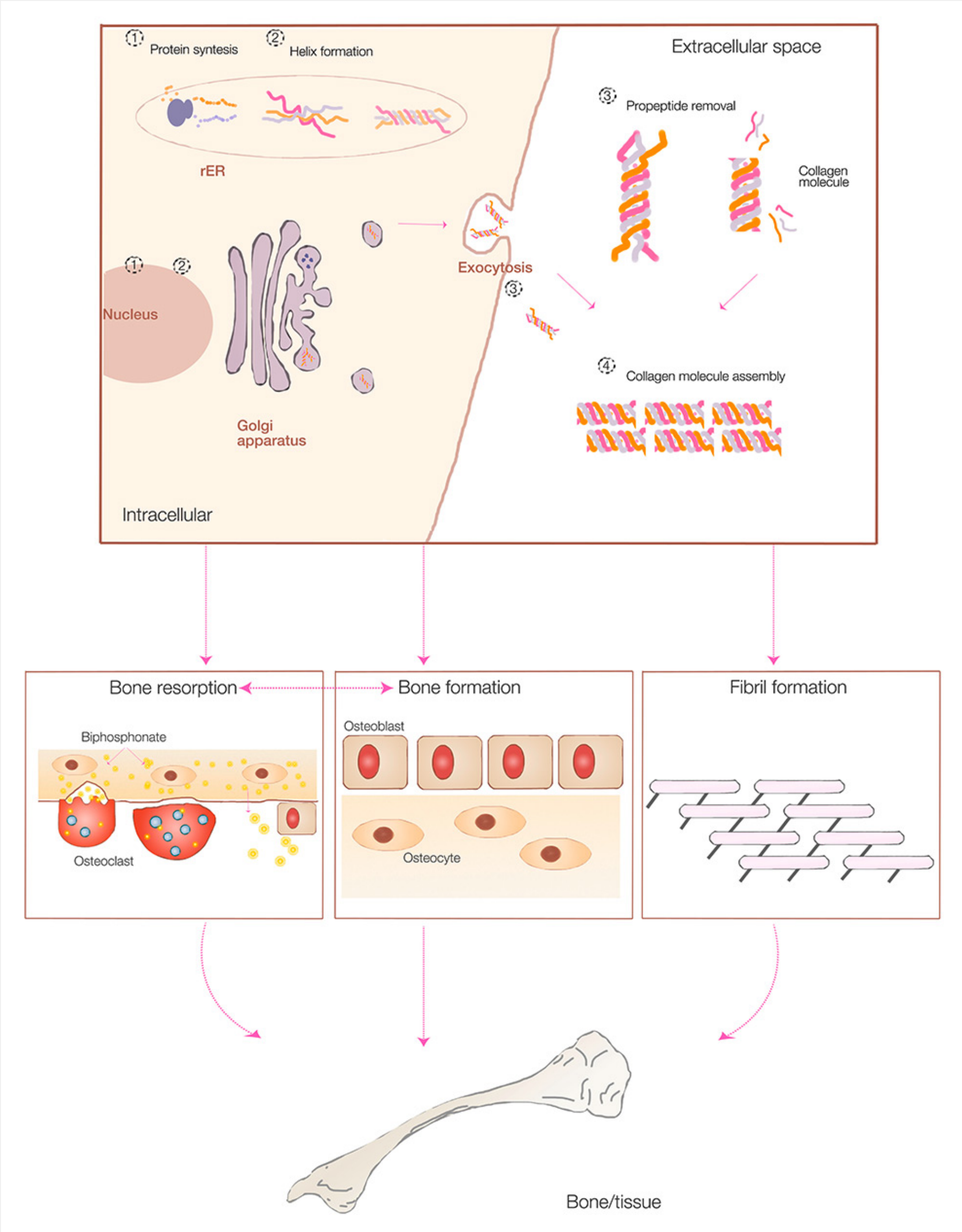

Figure 1

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 *CRTAP*, *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 1 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 osteoblasts, leads to a defect in bone formation. Bisphosphonates concentrate in the mineralised osseous matrix where they inhibit bone resorption by osteoclasts.

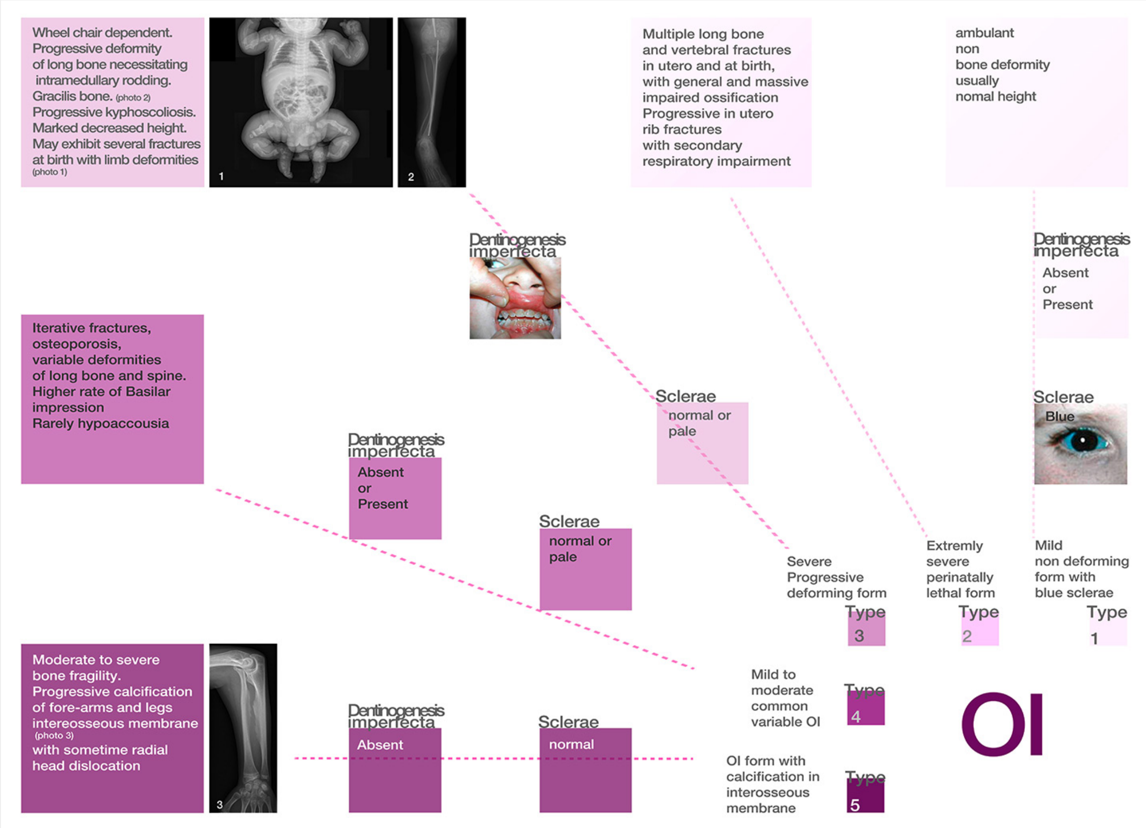

Figure 2

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