Osteogenesis imperfecta

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Abstract | Skeletal deformity and bone fragility are the hallmarks of the brittle bone dysplasia osteogenesis imperfecta. The diagnosis of osteogenesis imperfecta usually depends on family history and clinical presentation characterized by a fracture (or fractures) during the prenatal period, at birth or in early childhood; genetic tests can confirm diagnosis. Osteogenesis imperfecta is caused by dominant autosomal mutations in the type I collagen coding genes (*COL1A1* and *COL1A2*) in about 85% of individuals, affecting collagen quantity or structure. In the past decade, (mostly) recessive, dominant and X-linked defects in a wide variety of genes encoding proteins involved in type I collagen synthesis, processing, secretion and post-translational modification, as well as in proteins that regulate the differentiation and activity of bone-forming cells have been shown to cause osteogenesis imperfecta. The large number of causative genes has complicated the classic classification of the disease, and although a new genetic classification system is widely used, it is still debated. Phenotypic manifestations in many organs, in addition to bone, are reported, such as abnormalities in the cardiovascular and pulmonary systems, skin fragility, muscle weakness, hearing loss and dentinogenesis imperfecta. Management involves surgical and medical treatment of skeletal abnormalities, and treatment of other complications. More innovative approaches based on gene and cell therapy, and signalling pathway alterations, are under investigation.

Osteogenesis imperfecta — also known as brittle bone disease — is a phenotypically and genetically heterogeneous group of inherited bone dysplasias[1]. Although the primary clinical manifestation involves the skeleton, osteogenesis imperfecta is a generalized connective tissue disorder. Individuals with osteogenesis imperfecta have low bone mass and bone fragility, resulting in susceptibility to fractures of the long bones and vertebral compressions, variable deformity of long bones, ribs and spine, and substantial growth deficiency. An array of associated secondary features can be present, including blue sclerae, conductive or sensory hearing loss, dentinogenesis imperfecta, malocclusion, basilar invagination (that is, a developmental deformity that causes narrowing of the foramen magnum (the opening of the skull where the spinal cord passes through to the brain)), scoliosis, pulmonary function impairment, cardiac valve abnormalities, muscle weakness and ligamentous laxity[2] (FIG. 1).

Osteogenesis imperfecta had been known since the early 1980s as a dominantly inherited disease caused by mutations in either of the genes encoding type I collagen (that is, *COL1A1* and *COL1A2*), the main component of the extracellular matrix of bone and skin[1]. Since 2006, new mutations in collagen-related genes — with different inheritance patterns — have been found to cause osteogenesis imperfecta[3] (TABLE 1). Identification of these new causative genes has led to the adaptation of the original classification system for osteogenesis imperfecta (BOX 1; TABLE 1): the Sillence classification. In this Primer, we use the genetic classification outlined in TABLE 1 whenever referring to the type of osteogenesis imperfecta.

The causative mutation is identified in most patients, which provides a basis for genetic counselling. Understanding the genetic defects also increases the prospects for targeted therapies. In addition, most of the newly identified mutated genes encode proteins involved in pathways that were not previously known to be crucial for bone development. For example, prolyl 3-hydroxylation, the connected pathway between bone mineralization and vascular development, and regulated intramembrane proteolysis, which has been extensively studied for its effect on cholesterol metabolism, also affects bone[4]. As osteogenesis imperfecta has long served as a genetic model for severe osteopenia or osteoporosis, these discoveries have opened up new areas of bone research and enhanced interest in identifying the causative genes in the few remaining patients with unknown mutations.

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In this Primer, we provide an overview of epidemiology, genetics and pathophysiology of osteogenesis imperfecta, as well as diagnosis and management.

Epidemiology

Studies from Europe and the United States have found a birth prevalence of osteogenesis imperfecta of 0.3–0.7 per 10,000 births[5,6]. These birth cohort analyses reflect more-severe types of osteogenesis imperfecta and do not include more-subtle types that become apparent after birth. A population-based study that used the Danish National Patient Register found an annual incidence of osteogenesis imperfecta of 1.5 per 10,000 births between 1997 and 2013 (REF. 7). Population surveys in countries with comprehensive medical databases, such as Finland, estimated a prevalence of about 0.5 per 10,000 individuals[8], with most having phenotypically milder osteogenesis imperfecta type I and type IV (BOX 1; TABLE 1). Because these birth cohort and population surveys are based on clinical findings and tend to find mutually exclusive populations, a reasonable estimate of the incidence of osteogenesis imperfecta is about 1 per 10,000 individuals. Most patients are heterozygous for mutations in *COL1A1* or *COL1A2*. No difference in the prevalence between sexes was reported.

Approximately 90% of the 3,000 individuals whose mutations have been included in the osteogenesis imperfecta variant database (http://www.le.ac.uk/ge/collagen/) have alterations in either *COL1A1* or *COL1A2*, and the others have homozygous or biallelic mutations in one of the newly identified genes (TABLE 1). However, major sequencing centres offering a panel of causative mutations associated with osteogenesis imperfecta are identifying a lower frequency of structural *COL1A1* and *COL1A2* mutations in patients with moderate-to-severe disease. For example, of 598 individuals at the Shriners Hospital in Montréal, Canada, in whom mutations were identified, 77% had heterozygous alterations in *COL1A1* or *COL1A2*, 9% had a single mutation in *IFITM5* (osteogenesis imperfecta type V), and the remaining 12% had homozygous or biallelic mutations in other genes causing osteogenesis imperfecta[9]. Lethal collagen mutations may be under-represented in this population.

In populations with a high level of consanguinity or a high number of carriers, the incidence of osteogenesis imperfecta is higher than in outbred populations[10–12]. Among African Americans in the United States, for example, the carrier frequency for a single deleterious variant in *P3H1* (previously named *LEPRE1*; encoding prolyl 3-hydroxylase 1) is about 1 in 240 individuals[11]. Homozygosity for this so-called West African allele accounts for 25% of all infants with lethal osteogenesis imperfecta in this population and might be clinically misclassified as osteogenesis imperfecta type II. By contrast, among West Africans in Ghana and Nigeria, the carrier frequency for this allele is 1.5% and would result in an incidence of lethal recessive osteogenesis imperfecta equal to the incidence of *de novo* mutations in type I collagen[11]. Among First Nations people in northern Ontario, Canada, a single deep intronic variant results in the use of a cryptic exon that destabilizes the *CRTAP* (which encodes cartilage-associated protein) mRNA, and is responsible for the recessive osteogenesis imperfecta type VII[10,13]. As is the case for many recessive disorders, some populations harbour a single allele that accounts for the majority of individuals with a particular phenotype: a single exon deletion in *TMEM38B* found in individuals from Saudi Arabia[14]; a single frameshift in *FKBP10* found in individuals from Turkey[15]; and a missense mutation in *WNT1* in the Hmong people from Vietnam and China[16].

Mechanisms/pathophysiology

Defects in type I collagen

Collagen synthesis and processing. Type I collagen — the major protein component of the extracellular matrix in bone, skin and tendon — is mainly secreted by osteoblasts, dermal fibroblasts and tenocytes (FIG. 2). Despite the relatively simple structure of the collagen triple helix, the biosynthesis of type I procollagen is extremely complex, involving multiple steps and requiring an ensemble of proteins for post-translational modifications, folding, transport, secretion and quality control[17,18] (FIG. 3). The *COL1A1* and *COL1A2* transcripts are translated in the rough endoplasmic reticulum (rER), and the α(I)-chains undergo a series of post-translational modifications. Helical prolines in position Y of the Gly-Xaa-Yaa repeat (FIG. 2) are hydroxylated in position C4 by prolyl 4-hydroxylase 1 (P4H1), whereas specific prolines in the X positions are 3-hydroxylated by P3H1 and P3H2. Some lysine residues are hydroxylated by lysyl hydroxylases (LH1 and LH2), and glycosylation of hydroxylysines into galactosyl-hydroxylysine and glucosyl-galactosyl-hydroxylysine is catalysed by procollagen galactosyltransferase 1 and procollagen glucosyltransferase 1 (FIG. 3a). After synthesis of the carboxy-terminal propeptide, it forms intra-chain disulfide bonds and remains attached to the rER membrane (FIG. 3b). Selection and association of the correct chains into a triple helix occur by diffusion of the C-propeptides attached to the rER membrane. A nucleus for triple helix formation

is formed that staggers the chains in the correct order and initiates triple helix formation. Protein disulfide isomerase catalyses inter-chain disulfide bond formation, which stabilize the folding nucleus. Hydroxylation of proline residues and some lysine residues continues and triple helix formation proceeds from the C-terminal end towards the amino-terminal end. During this phase, 65 kDa FK506-binding protein (FKBP65; encoded by *FKBP10*) and a complex formed by P3H1 — CRTAP–PPIase B (peptidyl-prolyl *cis–trans* isomerase B) — seem to play a crucial part. The complex is involved in the hydroxylation of proline 986 of the collagen α1(I)-chain and α1(II)-chain and proline 707 of the α2(I)-chain[13,19–21], which are thought to be important for supramolecular assembly of collagen fibrils and to serve as binding sites for chaperones or small leucine-rich proteoglycans[22]. Beyond its prolyl 3-hydroxylase activity, the complex functions as a PPIase and chaperone for collagen folding[13,19,23]. Indeed, the fast propagation of the triple helix requires the isomerization of *cis* peptide bonds that convert proline residues into *trans* configuration, mainly by PPIase B[24] (FIG. 3c). When most of the helix is folded, the N-propeptides associate and form the small triple helix within this domain. The newly formed triple helix is stabilized by serpin H1 (also known as HSP47; encoded by *SERPINH1*) and FKBP65 (REFS 25–27). Further modifications occur during transport from the rER to the Golgi apparatus in special coat protein complex vesicles that contain melanoma inhibitory activity protein 3 (also known as TANGO1) and through the Golgi stack by cisternal maturation. Serpin H1 also has binding sites along the helical portion of the molecule and assists shuttling of folded collagen into the *cis*-Golgi[25–27]. These biosynthetic steps depend on a proper rER environment (for example, optimal calcium levels and redox potential), and the quality-control mechanisms can lead to the activation of the unfolded protein response using the ER-associated degradation pathway or the autophagy-mediated lysosomal degradation system to eliminate molecules that were not properly folded. Once secreted, the propeptides of procollagen are cleaved by a disintegrin and metalloproteinase with thrombospondin motifs 2 (ADAMTS2) and bone morphogenetic protein 1 (BMP1) into mature type I collagen. This initiates collagen fibre formation and these fibrils are stabilized by crosslink formation, in which certain lysine and hydroxylysine residues in the triple helix and the telopeptides are oxidized by lysyl oxidases and converted into allysine and hydroxyallysine. These residues then initially form divalent crosslinks that convert into mature trivalent pyridinoline and pyrrole crosslinks to stabilize the fibril structure in tissues (FIG. 3d).

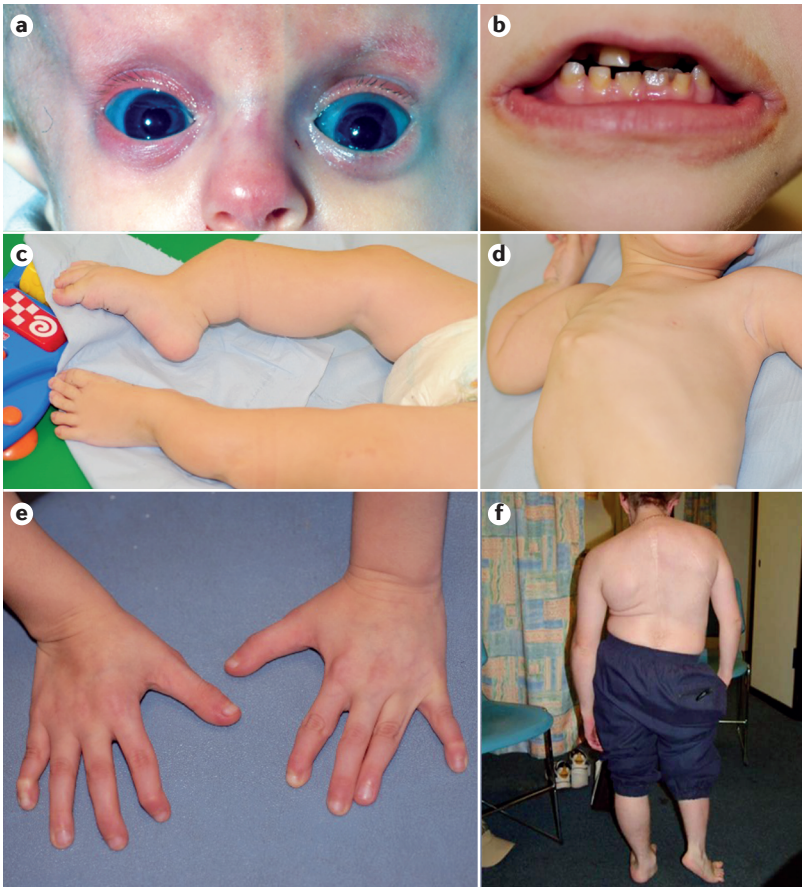

Figure 1 | **Clinical features associated with osteogenesis imperfecta.** Patients with osteogenesis imperfecta can present with an array of secondary features: blue sclerae (part **a**); dentinogenesis imperfecta (part **b**) characterized by dentin dysplasia, which results in weak and discoloured teeth; limb deformities (part **c**); pectus carinatum chest deformity (part **d**; also known as pigeon chest); clinodactyly (part **e**) characterized by an abnormal curvature of the fingers; and scoliosis (part **f**), as shown by the abnormal curvature of the spine. Images courtesy of M. Balasubramanian, University of Sheffield, Sheffield Children's NHS Foundation, UK.

Structural and quantitative collagen defects. Mutations in *COL1A1* and *COL1A2* can result in the synthesis of a reduced amount of normal type I collagen (quantitative defect) or in the production of collagen molecules with altered structure (structural defect)[1]. Quantitative defects are associated with the milder osteogenesis imperfecta type I, whereas structural collagen defects can cause the full range of moderate and progressive deforming type IV and type III, respectively, as well as lethal type II[28] (BOX 1; TABLE 1).

Structural mutations can lead to prolonged retention of the unfolded α(I)-chains in the ER, resulting in excessive modification of the collagen chains by exposing them to the post-translational-modifying enzymes for a longer time[17]. These overmodified collagen molecules assemble into abnormal fibrils, which results in aberrant extracellular matrix — one of the key features underlying bone fragility in osteogenesis imperfecta. In some cases, the abnormal collagen is partially retained in the ER, which causes ER stress and has been associated with autophagy stimulation, apoptosis activation and impaired osteoblast differentiation[29–32]. These abnormalities exacerbate matrix dysfunction and decrease collagen synthesis, which decreases bone mass[29].

The most common mutations causing structural collagen defects are single-nucleotide variants, substituting the glycine within the Gly-Xaa-Yaa repeat with a bulkier or charged residue. Some structural collagen defects (20–25%) are due to mutations in the 3′ or 5′ splice sites that are responsible for exon skipping

in *COL1A1* and *COL1A2* (REF. 1). If discrete collagen exons are skipped, the Gly-Xaa-Yaa triplet pattern is not altered, but chain alignment can be shifted, which affects folding and secretion[33]. Fewer than 5% of the mutations occur in the C-propeptide domain of procollagen, impairing chain association and/or causing folding delay[34]. An interesting and distinct group of helical structural defects are the consequence of duplication or deletion of one or two Gly-Xaa-Yaa triplets. Such mutations cause a register shift of the chains in the heterotrimeric molecule and are associated with lethal or severe osteogenesis imperfecta[35].

Table 1 | **Genetic classification of osteogenesis imperfecta**

Mutated gene	Encoded protein	Osteogenesis imperfecta type based on the genetic classification	Inheritance	OMIM	Clinical characteristics
Impairment of collagen synthesis and structure					
COL1A1 or *COL1A2*	Collagen α1(I) (COL1A1) or α2(I) (COL1A2)	I, II, III or IV*	AD	• 166200 • 166210 • 259420 • 166220	Classic phenotype (see BOX 1)
Compromised bone mineralization					
IFITM5	Bone-restricted interferon-induced transmembrane protein-like protein (BRIL; also known as IFM5)	V	AD	610967	Normal-to-severe skeletal deformity, intraosseous membrane ossifications, radiodense band and radial head dislocation, normal-to-blue sclerae and sometimes hearing loss
SERPINF1	Pigment epithelium-derived factor (PEDF)	VI	AR	613982	Moderate-to-severe skeletal deformity, the presence of osteoid, fish-scale appearance of lamellar bone pattern and childhood onset
Abnormal collagen post-translational modification					
CRTAP	Cartilage-associated protein (CRTAP)	VII	AR	610682	Severe rhizomelia with white sclerae
P3H1 (previously known as *LEPRE1*)	Prolyl 3-hydroxylase 1 (P3H1)	VIII	AR	610915	
PPIB	Peptidyl-prolyl *cis–trans* isomerase B (PPIase B)	IX	AR	259440	Severe bone deformity with grey sclerae
Compromised collagen processing and crosslinking					
SERPINH1	Serpin H1 (also known as HSP47)	X	AR	613848	Severe skeletal deformity, blue sclerae, dentinogenesis imperfecta, skin abnormalities and inguinal hernia
FKBP10	65 kDa FK506-binding protein (FKBP65)	XI	AR	610968	Mild-to-severe skeletal deformity, normal-to-grey sclerae and congenital contractures
PLOD2	Lysyl hydroxylase 2 (LH2)	No type	AR	609220	Moderate-to-severe skeletal deformities and progressive joint contractures
BMP1	Bone morphogenetic protein 1 (BMP1)	XII	AR	614856	Mild-to-severe skeletal deformity and umbilical hernia
Altered osteoblast differentiation and function					
SP7	Transcription factor SP7 (also known as osterix)	XIII	AR	613849	Severe skeletal deformity with delayed tooth eruption and facial hypoplasia
TMEM38B	Trimeric intracellular cation channel type B (TRIC-B; also known as TM38B)	XIV	AR	615066	Severe bone deformity with normal-to-blue sclerae
WNT1	Proto-oncogene Wnt-1 (WNT1)	XV	• AR • AD	• 615220 • Unknown	Severe skeletal abnormalities, white sclerae and possible neurological defects
CREB3L1	Old astrocyte specifically induced substance (OASIS; also known as CR3L1)	XVI	AR	616229	Severe bone deformities
SPARC	SPARC (also known as osteonectin)	XVII	AR	616507	Progressive severe bone fragility
MBTPS2	Membrane-bound transcription factor site-2 protease (S2P)	XVIII	XR	Unknown	Moderate-to-severe skeletal deformity, light blue sclerae, scoliosis and pectoral deformities

AD, autosomal dominant; AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org); XR, X-linked recessive.
*Classic types of osteogenesis imperfecta, as outlined in BOX 2.

Box 1 | **Classification of osteogenesis imperfecta**

The classic classification of osteogenesis imperfecta — proposed by Sillence *et al.*[134] in 1979 — has been the standard for over two decades. Sillence types I–IV are typically regarded as classic osteogenesis imperfecta. They are caused by dominantly inherited mutations in genes encoding type I collagen (*COL1A1* and *COL1A2*), and classification is based on clinical presentation, radiographic features and patterns of inheritance.

- Type I: characterized by blue sclerae, near-normal stature, and late-onset hearing loss, but without apparent dentinogenesis imperfecta
- Type II: a perinatally lethal form
- Type III: a progressive deforming variety
- Type IV: characterized by white sclerae, short stature, bone deformity and dentinogenesis imperfecta, which is more severe than type I but less severe than type II and type III

Genetic understanding of osteogenesis imperfecta has led to two new approaches to classification: a more clinically based approach in which the new recessive types are put under the Sillence-type clinical umbrella, or a genetic–functional approach in which the Sillence types I–IV are reserved for mutations in *COL1A1* or *COL1A2* and new genes are given additional type numbers based on the mutation without clinical correlation. We use this genetic classification — outlined in TABLE 1 — when referring to osteogenesis imperfecta types throughout.

The position of the mutations along the chain, the nature of the substituting amino acid as well as the particular chain in which the substitution occurs affect clinical outcome[1]. Owing to the C-terminal to N-terminal end direction of the zipper-like folding of the three α-chains (FIG. 3c), mutations in the triple helical N-terminal 200 residues minimally disturb helix formation and are generally associated with non-lethal phenotypes, whereas mutations in the C-terminal helical region cause both lethal and moderate outcomes. Substitutions with branched-chain or charged amino acids are responsible for severe phenotypes. In general, a smaller proportion of mutations in *COL1A2* cause lethal osteogenesis imperfecta than do mutations in *COL1A1*, often attributed to the type I collagen stoichiometry that implies the presence of a mutant chain in 75% and 50% of collagen triple helices from defects in α1 and α2, respectively. The three major ligand-binding regions (MLBRs; FIG. 2) identified along the α1(I)-chain[36] are particularly important for matrix quality. The C-terminal MLBR3 is especially crucial for interactions of collagen with extracellular matrix proteins; substitutions in this domain impair extracellular matrix organization and have predominantly lethal outcomes[36,37]. Mutations in the C-propeptide that impair α-chain recognition are responsible for ER-associated protein degradation activation, which favours the removal of unassembled chains[29]. In the α2(I)-chain, lethal regions that align with proteoglycan-binding sites on collagen fibrils have been identified along the chain; mutations in these domains may severely affect proper matrix assembly[36,37].

Collagen processing defects. Extracellular cleavage of the propeptide is necessary for spontaneous collagen assembly and the formation of fibrils and fibres in the extracellular space[38] (FIGS 2,3). Dominant mutations affecting either the C-propeptide or N-propeptide cleavage sites or recessive mutations affecting the activity of the enzymes catalysing cleavage (that is, BMP1 and ADAMTS2) result in distinctive phenotypes (TABLE 1).

Dominant mutations affecting the first 90 N-terminal amino acids of the collagen helix in either the α1(I)-chain or in the α2(I)-chain alter the tertiary structure of the N-propeptide cleavage site without altering its sequence, which makes the site unrecognizable as an ADAMTS2 substrate. The resulting pN-collagen (that is, the mature collagen with the N-propeptide attached) assembles into small diameter fibrils with regular borders[39,40]. Retention of the N-propeptide in the collagen molecule might also compromise the intracellular functions of the propeptide, such as protein phosphorylation, collagen synthesis and cell adhesion[41,42]. Furthermore, the N-propeptide in the extracellular matrix binds to specific cytokines (for example, transforming growth factor-β1 (TGFβ1) and BMP2), which are crucial for bone development[42]. Mutations that remove the N-terminal cleavage site residues due to exon skipping[43] cause Ehlers–Danlos syndrome, and not osteogenesis imperfecta (BOX 2).

Dominant mutations that affect the α1(I) and α2(I) C-terminal cleavage site or recessive mutations that cause defects in BMP1 (FIG. 2) result in the presence of pC-collagen (that is, the mature collagen with the C-propeptide attached) in the extracellular matrix[44–47]. Mutations that impair the cleavage site of the C-propeptides cause a mild osteogenesis imperfecta with normal or increased z-scores (indicating normal or increased bone mineral density) measured by dual-energy X-ray absorptiometry. Mutations in *BMP1* result in more-severe forms of osteogenesis imperfecta than cleavage site mutations, as BMP1 broadly affects extracellular matrix assembly and structure by processing the C-propeptides of type I and type III collagen[48,49], N-propeptides of pro-α1(V) and pro-α1(XI)[50,51], cleavage of the collagen and elastin crosslinking enzyme pro-lysyl oxidase[52] and of small leucine-rich proteoglycans, such as prodecorin and probiglycan[53,54]. BMP1 is also responsible for the activation of multiple cytokines, such as TGFβ1, BMP2 and BMP4 (REF. 55). The presence of pC-collagen affects fibril structure, favouring an abnormal high mineralization that is associated with bone fragility and leads to a paradoxical high bone mass osteogenesis imperfecta. Hypermineralization might be the consequence of increased inter-fibrillar spacing and a direct effect of pC-collagen as a mineral nucleator. Mutations that cause substitution in the cleavage site residues in pro-α1(I) cause fibrils with limited blebbing and almost normal diameter, whereas substitutions in pro-α2(I) cleavage site residues yield thin fibres with multiple blebs, probably owing to protruding C-propeptide, which may be differentially digested by nonspecific proteases[44].

Defects in collagen post-translational modification. The crucial role of post-translational modification and proper folding of type I procollagen in the pathogenesis of osteogenesis imperfecta emerged from the identification of patients with recessive mutations in genes encoding proteins that have an important role in these processes, for example, CRTAP[13,56], P3H1 (REF. 57) and PPIase B[58] (FIG. 3; TABLE 1).

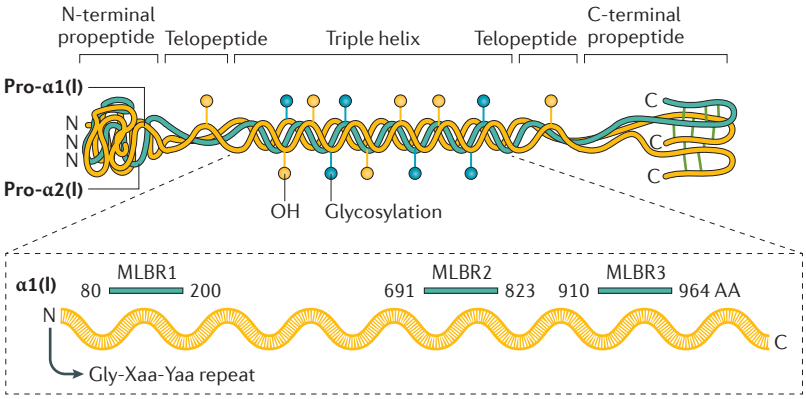

Figure 2 | **Structure of collagen.** Type I collagen is a heterotrimer composed of two α1 and one α2 left-handed polyproline II-like chains that are assembled into a right-handed triple helix. It is synthesized as a procollagen, containing both amino-terminal and carboxyl-terminal propeptide sequences, which are proteolytically cleaved by specific proteases (a disintegrin and metalloproteinase with thrombospondin motifs 2 (ADAMTS2) and bone morphogenetic protein 1 (BMP1), respectively) that recognize a sequence in the telopeptides, that is, p.Pro161Gln162 in α1(I) and p.Ala79Gln80 in α2(I) for the N-terminal cleavage sites, and p.Ala1218Asp1219 and p.Ala1119Asp1120 for the C-terminal cleavage sites[242]. The sequence of each collagen chain is characterized by Gly-Xaa-Yaa repeats (in which X and Y can be any amino acid (AA) but are most often proline and hydroxyproline). Glycine is required at every third position and is tightly packed at the centre of the triple helical structure. Collagen contains ~20% proline residues. The post-translational 4-hydroxylation of most prolines in the Yaa position is required for triple helical stability[243]. Along the α1-chain, specific regions that are relevant for the interaction of collagen with other collagen molecules or with extracellular matrix proteins were identified, namely, major ligand-binding region (MLBR).

Homozygous or biallelic *CRTAP*-null mutations[56] were identified in patients displaying a phenotype that overlapped with, but was distinct from, osteogenesis imperfecta type II and type III (BOX 1). CRTAP deficiency causes a severe-to-lethal osteochondrodysplasia with rhizomelia (that is, a disproportion of limb segments, in which the proximal segment is relatively short), neonatal fractures, broad undertubulated (that is, cylindrical configuration from lack of diaphyseal modelling) long bones and fragile ribs. Occasional survivors have severe growth deficiency and popcorn calcifications of epiphyses. CRTAP deficiency causes severely reduced hydroxylation of proline 986 of the α1(I)-chain and delayed helix folding and consequent overmodification of the type I collagen helical region by LH1 and P4H1 (REFS 13,56). *Crtap*-knockout mice exhibit a severe osteochondrodysplasia[13].

Absence of either CTRAP or P3H1 results in the absence of the activity of both[59] because the proteins are mutually protective (FIG. 3). As such, *P3H1*-null mutations give rise to a phenotype that is clinically indistinguishable from CRTAP deficiency. Biochemically, severely reduced hydroxylation of proline 986 of the α1(I)-chain and type I collagen overmodification[57,60,61], and an unanticipated 50% increase in collagen production versus controls are observed in patients with *P3H1* mutations[57].

Defects in PPIase B (FIG. 3) result in a more variable clinical and biochemical phenotype that overlaps with that caused by *CRTAP* and *P3H1* mutations, except for the absence of rhizomelia[58,61–63]. In two patients, a moderate osteogenesis imperfecta phenotype was described[64], which was associated with normal 3-hydroxylation of proline 986 of the α1(I)-chain and normal helical folding, whereas in others, hydroxylation of proline 986 of the α1(I)-chain was reduced to a lesser extent than patients with CRTAP and P3H1 deficiency, and collagen overmodification was observed[58]. These findings suggest that collagen modification is dependent on the *PPIB* mutation.

Defects in collagen chaperones and crosslinking. When folding of the major helix is completed, molecular chaperones (serpin H1 and FKBP65) interact with type I procollagen to prevent premature fibril formation within the rER[24,65,66] (FIG. 3). Serpin H1 stabilizes the folded procollagens in the rER and assists their shuttling into the *cis*-Golgi[25–27]. FKBP65 also has PPIase activity[24].

Only four different homozygous *SERPINH1* missense mutations have been described, one in Dachshunds and three in humans, all resulting in moderate-to-severe osteogenesis imperfecta[67] (TABLE 1). These mutations are located in the serine-type endopeptidase inhibitor domain of serpin H1, which is crucial for chaperone function, leading to intracellular retention of type I collagen. In affected humans and dogs, 3-hydroxylation of proline 986 of the α1(I)-chain is normal. Post-translational overmodification of type I collagen is absent in humans but present in dogs, which also show abnormal collagen crosslinks in bone and ER stress[68]. The milder phenotype in humans probably results from residual serpin H1 function. *Serpinh1*-null mice are embryonically lethal[69], owing to aggregation of improperly folded collagen in the rER, delayed collagen secretion and eventually defective collagen fibrillogenesis[70].

Defects in FKBP65 result in a range of overlapping phenotypes, including moderate-to-severe osteogenesis imperfecta, Bruck syndrome (characterized by severe osteogenesis imperfecta with congenital contractures) and Kuskokwim syndrome (congenital contractures with minimal skeletal involvement)[15,61,71–78]. Remarkable phenotypic variability is observed, even within families. Collagen secreted from FKBP65-defective cells shows normal 3-hydroxylation of proline 986 of the α1(I)-chain and normal-to-only-slightly overmodified helical modifications, but C-telopeptide lysine residues that are crucial for collagen crosslinking[18,79] are severely underhydroxylated[76]. The hydroxylation of C-telopeptide lysine residues is catalysed by LH2, deficiency of which mainly leads to Bruck syndrome, but also to forms of recessive osteogenesis imperfecta without contractures[80–82]. How FKBP65 decreases LH2 activity is not yet understood. Deficiency of the FKBP65 chaperone or PPIase functions may block the activation of LH2 or the telopeptide structure[76].

Defects in bone formation and mineralization

Impaired bone mineralization. Some types of osteogenesis imperfecta are not caused by mutations that affect the collagen pathway itself, but by mutations in genes involved in bone mineralization and in the differentiation of osteoblasts (FIG. 4; TABLE 1).

Osteogenesis imperfecta type VI is caused by recessive null mutations in *SERPINF1*, which encodes pigment epithelium-derived factor (PEDF). PEDF is an anti-angiogenic factor that also interacts with receptor activator of nuclear factor-κβ ligand (RANKL; also known as TNFSF11) pathway, thereby increasing the activity of osteoclasts[83–85] (FIG. 4a). Absence of PEDF leads to broad osteoid (unmineralized bone matrix) seam in bone, which indicates delayed mineralization.

Osteogenesis imperfecta type V is caused by a recurring dominant mutation in the 5′ untranslated region of *IFITM5*, creating a new start codon and elongating the N terminus of bone-restricted interferon-induced transmembrane protein-like protein (BRIL; also known as IFM5) by five amino acids. Type V is the only dominant type of osteogenesis imperfecta beside the classic types caused by mutations in *COL1A1* and *COL1A2* (REFS 86,87). BRIL seems to have a crucial role during bone mineralization. Interestingly, mutations in the gene that encodes BRIL seem to have a gain-of-function effect if the protein is elongated, inducing increased bone formation, which leads to hyperplastic callus and ossification of membranes, whereas mutations in the coding regions impair mineralization of bone[86,88].

The interaction between PEDF and BRIL became evident in patients with a p.S40L substitution in *IFITM5*. These patients presented with a severe atypical clinical course and histomorphometric and laboratory findings consistent with patients with osteogenesis imperfecta type VI[88,89]. The amount of osteoid was increased and the production of PEDF in osteoblasts was decreased. These findings support the hypothesis that BRIL and PEDF interact in the process of osteoblast development, osteoid formation and mineralization, but the exact mechanisms remain to be elucidated.

Patients with osteogenesis imperfecta type V have overall brittle bone with a similar severity compared with patients with osteogenesis imperfecta type IV, but bone abnormalities are marked by a triad of hyperplastic callus formation, radiodense lines at the epiphyses and calcification of the interosseous membrane of the forearm[90]. Patients with osteogenesis imperfecta type V may also have radial dislocation, but do not have the scleral or dental findings of osteogenesis imperfecta associated with defects in the quantity, structure or processing of type I collagen. Bone tissue histomorphometry is also distinct, with a mesh-like lamellation pattern under polarized light. By contrast, patients with osteogenesis imperfecta

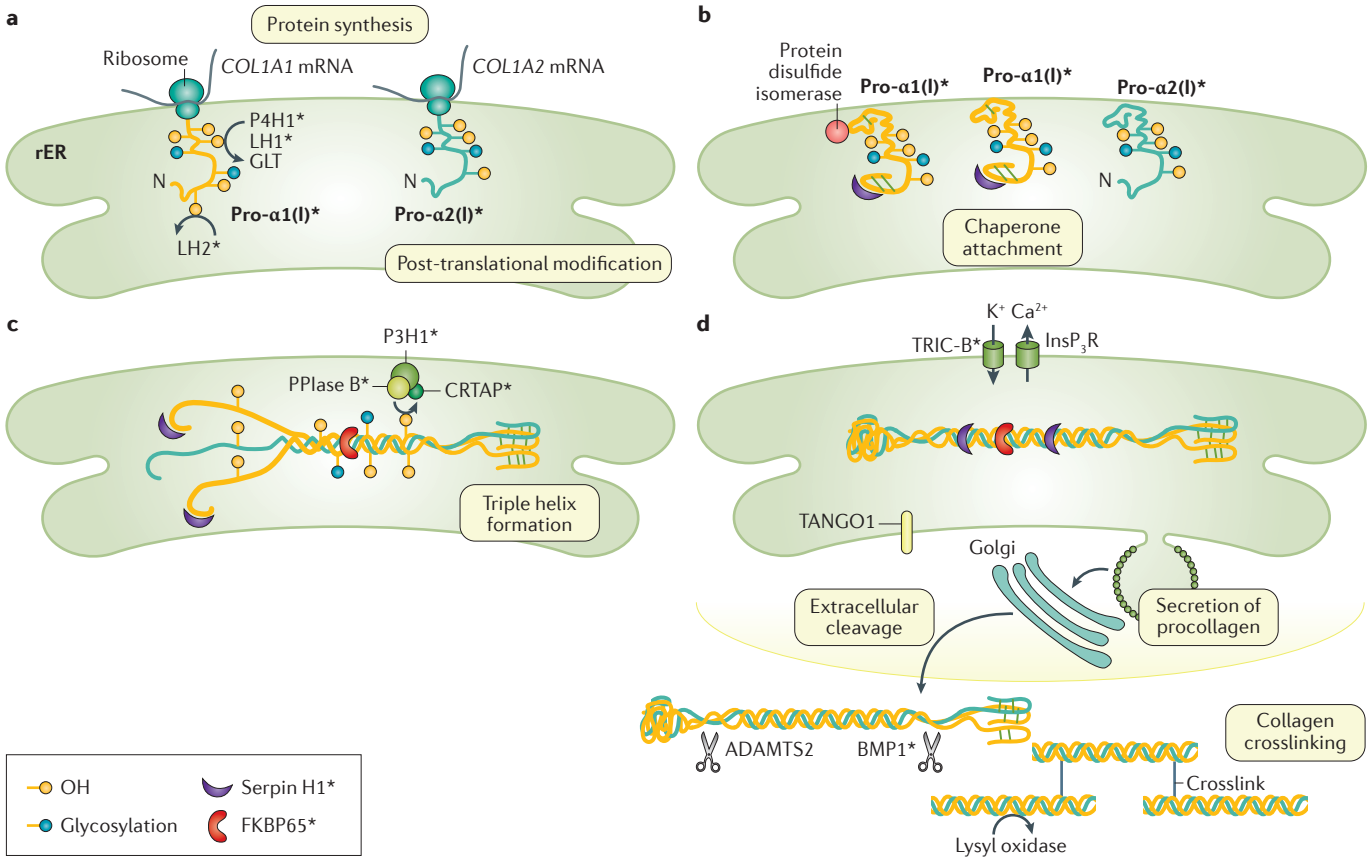

Figure 3 | **Type I collagen synthesis and processing. a** | Translation and post-translational modifications of pro-α1(I) and pro-α2(I). **b** | Interactions with molecular chaperones to prevent premature triple helix formation. **c** | Triple helix formation that comprises two pro-α1-chains and one pro-α2-chain. **d** | Secretion of procollagen, extracellular cleavage to collagen and crosslinking. ADAMTS2, a disintegrin and metalloproteinase with thrombospondin motifs 2; BMP1, bone morphogenetic protein 1; CRTAP, cartilage-associated protein; GLT, galactosyltransferase 1; $InsP_3R$, inositol-1,4,5-triphosphate receptor; LH, lysyl hydroxylase; P3H1, prolyl 3-hydroxylase 1; P4H1, prolyl 4-hydroxylase 1; PPIase B, peptidyl-prolyl *cis–trans* isomerase B; rER, rough endoplasmic reticulum; TANGO1, transport and Golgi organization protein 1; TRIC-B, trimeric intracellular cation channel type B. *Mutations in the genes encoding these proteins are associated with osteogenesis imperfecta.

Box 2 | **Ehlers–Danlos syndrome**

Absence of the amino-terminal cleavage site in pro-α1(I) and pro-α2(I) causes Ehlers–Danlos syndrome (EDS) VIIA or VIIB, respectively, rather than osteogenesis imperfecta[43]. EDS is a connective tissue disease characterized by skin and joint laxity with vascular symptoms in some types. Although these patients have mild osteopenia, their main clinical characteristics are severe joint hypermobility, dislocations and ligamentous laxity. The matrix fibres contain pN-collagen (that is, the mature collagen with the N-propeptide attached), causing irregular borders and reduced diameter. Defects in *ADAMTS2* cause EDS VIIC, which is associated with extreme skin fragility[239]. In this recessive condition, not only type I collagen processing but also the processing of other fibrillar collagen types, such as type II collagen[240], are compromised, complicating the molecular consequence of the mutations.

type VI are mostly mildly affected at birth, exhibit progressive brittle bone disease and often have considerable increased serum levels of alkaline phosphatase (a marker for osteoblast activity) in childhood. Their bone histomorphometry is distinct, with increased amounts of unmineralized osteoid and a fish-scale pattern under polarized light. Patients with osteogenesis imperfecta type VI have a poor response to bisphosphonate (an anti-resorptive) treatment[91].

Defects in osteoblast differentiation and function. Genes involved in osteoblast differentiation have recently been associated with osteogenesis imperfecta, although, for most, the underlying pathogenetic mechanism remains to be determined (TABLE 1). A hypomorphic mutation (partial loss of function) in *SP7*, encoding the osteoblast-specific transcription factor SP7 (also known as osterix), which is essential for bone formation, was described in a child with recessive osteogenesis imperfecta[92]. *Sp7*-null mice show deficient osteoblast differentiation and proliferation, and reduced expression of osteoblast markers[93].

Defects in trimeric intracellular cation channel type B (TRIC-B; also known as TM38B and encoded by *TMEM38B*) were found in patients with moderate osteogenesis imperfecta[14,94] (FIG. 4b). TRIC-B is a monovalent cation-specific channel that is necessary for intracellular calcium flux and is involved in cell differentiation[95]. *Tmem38b*$^{-/-}$ mice are neonatally lethal and have reduced bone volume[95,96]. Defective ER calcium flux dysregulates collagen synthesis by multiple ER enzymes[94,97] (FIG. 3d).

Homozygous mutations in *WNT1* were identified in patients with moderate-to-severe, progressive osteogenesis imperfecta. Heterozygous *WNT1* mutations lead to osteoporosis[16,98–100]. WNT1 interacts with the receptor Frizzled and its co-receptor low-density lipoprotein receptor-related protein 5/6 (LRP5/6) to activate bone formation[101,102] (FIG. 4b). Homozygous or biallelic *LRP5* loss-of-function mutations cause osteoporosis-pseudoglioma syndrome[103–105], whereas heterozygous gain-of-function mutations cause van Buchem disease type 2 (or endosteal hyperostosis)[106]. *Wnt1*$^{-/-}$ mice are embryonically lethal and have severe brain abnormalities but no reported skeletal phenotype, whereas the Swaying mouse (which is homozygous for a single-nucleotide deletion in *Wnt1* in exon 3) survives postnatally, has severe osteopenia and a cerebellar defect, similar to some human *WNT1* mutations[99,107].

Finally, two genes encoding proteins that are part of the regulated intramembrane proteolysis (RIP) pathway in osteoblasts have been reported to cause osteogenesis imperfecta (FIG. 4b). In RIP, the endopeptidases S1P (encoded by *MBTPS1*) and S2P (encoded by *MBTPS2,* the first identified X-linked gene for osteogenesis imperfecta) in the Golgi membrane sequentially cleave regulatory proteins transported from the ER membrane in times of ER stress or sterol metabolite deficiency. Mutations that cause single-residue substitutions in or near the ion-coordination site of S2P, and impair its cleavage of substrate transcription factors, have been reported in two pedigrees with moderate-to-severe osteogenesis imperfecta. Hydroxylation of lysine 87 of the α1(I)-chain and α2(I)-chain is reduced, collagen crosslinking is altered and bone strength is impaired in bone tissues of patients with *MBTPS2* mutations[108]. One of the transcription factors activated by RIP is old astrocyte specifically induced substance (OASIS; encoded by *CREB3L1*) (FIG. 4b). Deficiency of OASIS was reported in a family with severe-to-lethal osteogenesis imperfecta[109]. OASIS is an ER stress transducer that regulates the transcription of genes involved in developmental processes, differentiation and maturation. *Creb3l1*$^{-/-}$ mice display severe osteopenia with spontaneous fractures and decreased type I collagen production in bone[110].

Bone tissue characteristics

The hallmark feature of osteogenesis imperfecta is high bone fragility that arises from low bone mass and abnormalities in bone material properties, such as reduced toughness. Alterations in bone tissue characteristics are surprisingly similar in most types of osteogenesis imperfecta. At the microscopic scale, histomorphometric studies showed that the decrease in bone mass is mirrored by a decrease in cortical width and cancellous bone volume in children who have classic Sillence osteogenesis imperfecta (BOX 1), as well as in recessive type VII and type VIII. However, nearly independent of the clinical outcome, bone turnover is increased owing to the presence of a higher number of osteoblasts and osteoclasts, whereas matrix production at the single cell level is markedly reduced[10,90,111,112].

The degree of mineralization of the bone matrix, determined by measurements of the bone mineralization density distribution using quantitative backscattered electron imaging, was found to be almost universally increased in osteogenesis imperfecta[113]. Consistently, biopsy samples from children with a mild phenotype and either qualitative or quantitative *COL1A1* or *COL1A2* mutations revealed a similar increase in mean calcium content of the bone matrix[114]. The same is true in patients with a more severe phenotype (type IV and type III) and in recessive type VII and type VIII[112,115,116]. Interestingly, in type VI, highly mineralized bone areas are surrounded by fringes that show low mineral content and abnormally mineralizing young osteocytes[117]. The increased mineral content in bone of patients with osteogenesis imperfecta is unchanged by bisphosphonate treatment[112,115,118]. In samples from children with mild osteogenesis imperfecta and from mouse models studied

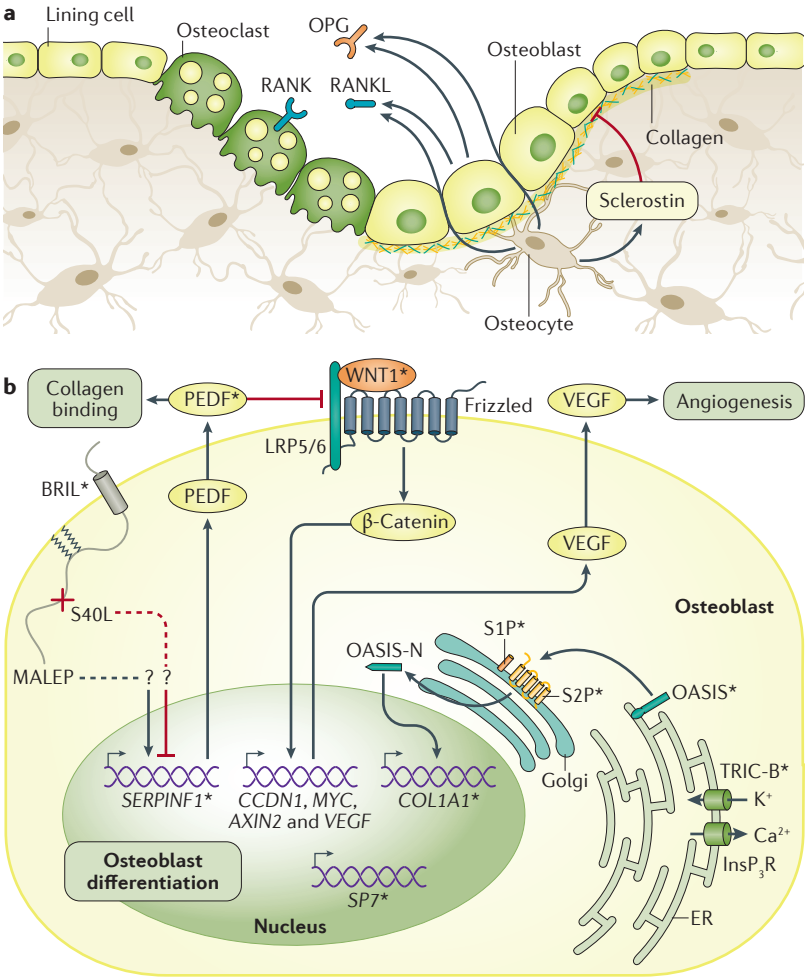

Figure 4 | **Defects in bone formation and mineralization in osteogenesis imperfecta. a** | Bone remodelling. Bone formation consists of the secretion of bone extracellular matrix components (mainly type I collagen) by osteoblasts. The unmineralized bone matrix (osteoid) subsequently becomes mineralized. In addition, osteoblasts and osteocytes release many cytokines, including receptor activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11) and osteoprotegerin (OPG), which regulate bone resorption by osteoclasts. RANKL acts on osteoclast precursor cells by binding to receptor activator of nuclear factor-κB (RANK; also known as TNFRSF11A) on their surface, thereby favouring their differentiation to osteoclasts. OPG, by interacting with RANKL, prevents the binding of RANKL to RANK. Some osteoblasts become embedded in the mineralized bone matrix and differentiate to osteocytes, which produce, among other factors, sclerostin, an inhibitor of the WNT pathway that is known to stimulate bone formation by stimulating osteoblast activity. **b** | WNT1 is a secreted ligand that stimulates the transcription of genes involved in osteoblast differentiation by interacting with the receptors low-density lipoprotein receptor-related protein 5/6 (LRP5/6) and Frizzled on osteoblast precursor cells. Endopeptidase S2P is a protease in the Golgi membrane that is involved in regulated intramembrane proteolysis (RIP) of transcription factors, such as old astrocyte specifically induced substance (OASIS), which is transported from the endoplasmic reticulum (ER) membrane for processing in times of ER stress. Pigment epithelium-derived factor (PEDF) is a multifunctional secreted protein with anti-angiogenic activity; bone-restricted interferon-induced transmembrane protein-like protein (BRIL) is a transmembrane protein involved in mineralization. Crosstalk between the two proteins had been elucidated following mutations identified in patients with osteogenesis imperfecta. Dashed lines indicate unknown pathways. $InsP_3R$, inositol-1,4,5-triphosphate receptor; OASIS-N, N-terminal part of OASIS; MALEP, methionine, alanine, leucine, glutamate and proline pentapeptide; S40L, p.Ser40Leu substitution; TRIC-B, trimeric intracellular cation channel type B; VEGF, vascular endothelial growth factor. *Mutations in the genes encoding these proteins are associated with osteogenesis imperfecta.

by small-angle X-ray scattering, the thickness of bone mineral particles was the same or smaller than in controls[119,120]. The combination of increased matrix mineral content and similar particle size implies that mineral particles are more-tightly packed in the extracellular matrix. As the extracellular matrix contains mostly collagen, the total space left for water between collagen molecules and mineral particles is decreased in osteogenesis imperfecta[121], making the bone stiffer. Moreover, collagen crosslinks are altered, which is also likely to increase the brittleness of the bone tissue[122,123].

Resistance to fracture, quantitatively determined in mouse models of osteogenesis imperfecta such as in osteogenesis imperfecta murine (oim) mice (carrying a point mutation in *Col1a2* in the region encoding the C-propeptide, preventing the incorporation of the α2(I)-chain into the collagen heterotrimer) and brittle IV (Brtl/+) mice (a point mutation in *Col1a1* that causes the Gly349Cys substitution in the α1(I)-chain and the synthesis of an overmodified type I collagen), was found to be reduced[124,125]. The increased vulnerability to fractures might be explained by abnormalities of the mineralized matrix at different levels, affecting structures that normally hinder crack propagation[126]. First, compared with controls, the alignment of collagen fibrils was found to be more disordered and less lamellar in both oim mouse models[124,127] and biopsy samples from patients with osteogenesis imperfecta[128]; second, the collagenous matrix is not only reduced in amount[129] but also showed more non-enzymatic crosslinks[124]; third, unmineralized collagen fibrils from the oim mouse model showed reduced strength under tensioning[130] and more affinity to water[131]. By contrast, less tissue water was found in fully mineralized bone of the oim mice[132] and in bone biopsies from patients with osteogenesis imperfecta[121]. Last, this is in good agreement with the increased amount of mineral in the matrix, corresponding to a higher density of thinner mineral platelets in both oim mouse models[124,127] and patients with osteogenesis imperfecta[120]. The cooperative effect of these secondary defects on bone fragility is probably more important than the collagen mutation itself, as discussed in a recent review[133].

Mechanical testing shows that bone is generally less stiff, allowing it to bend with less force and reducing the load to reach a point of non-recoverable deformity or fracture; these characteristic contribute to the exacerbation of bone deformity, just by the pull of normal muscle, and bone fractures. Most crucially, bone in osteogenesis imperfecta is a brittle tissue and cannot dissipate energy efficiently; although healthy bone can absorb energy into the extracellular matrix with advancing deformation, osteogenesis imperfecta bone snaps like chalk with minimal displacement[133].

Diagnosis, screening and prevention

Classification

The modern era of classification of osteogenesis imperfecta began with clinical studies by David Sillence and colleagues in the late 1970s[134] that recognized four distinct groups standardized as 'types' on the basis of clinical presentation, radiographic features and patterns of

inheritance. After the past decade of advances in genetics, two approaches to classification have evolved (BOX 1). We use the genetic–functional approach, in which the Sillence types I–IV (classic osteogenesis imperfecta) are reserved for mutations in *COL1A1* or *COL1A2*, and new genes are given additional type numbers (TABLE 1).

One of the advantages of the genetic classification is that patients and families know the cause of the disease and they quickly understand that not all types are the same, even though they have common features. A genetic classification provides an inheritance pattern for counselling, and functional groupings for natural history and treatment research. Unlike in a clinical classification, the genetic 'type' of an individual will not change as they age or between family members. The Online Mendelian Inheritance in Man database has used a mixed classification, with types I–IV according to the Sillence classification[134], and the remainder classified by type number and gene with some elements of clinical differentiation. The Osteogenesis Imperfecta Foundation has adopted a genetic–functional classification based on Forlino *et al.*[4], in which genes are linked to numerical types and grouped by similarity of function (TABLE 1).

By contrast, the advantages of the clinical classification are that most assessments and decisions about treatment are made on clinical grounds (even though there is evidence that bisphosphonates, for example, are less effective in individuals with mutations in *SERPINF1* and with some mutations in other genes) and so the value of gene-based classification may be limited. This has led to the creation of a classification based largely on the ability to identify groups on clinical grounds (clinical classification) suggested by the working group of the International Skeletal Dysplasia Society, with subclasses defined by the pattern of inheritance and the host gene[135]. An additional type was added — type V — characterized by osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus.

Classification of the different types of osteogenesis imperfecta is still debated, in particular, the generation of a classification scheme that does not change criteria for emerging types.

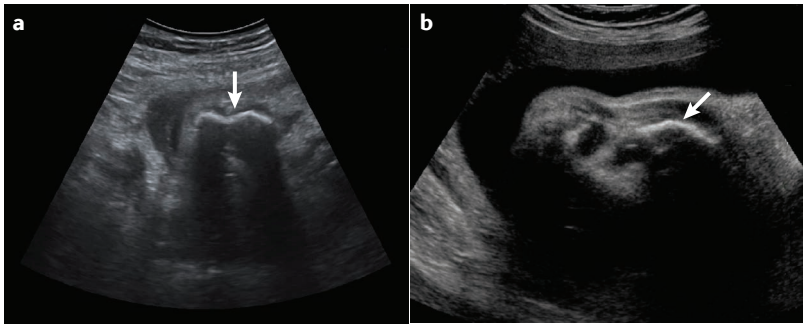

Figure 5 | **Prenatal screening for osteogenesis imperfecta.** Ultrasonography images of two fetuses at 32 weeks (part **a**) and 33 weeks (part **b**) of gestation with genetically proven osteogenesis imperfecta demonstrating a severe bowing of the femur (arrows) in both cases and probably an intrauterine fracture in one of them (part **a**).

Diagnosis

The diagnosis of osteogenesis imperfecta usually depends on clinical presentation (FIG. 1), including a (prenatal) fracture (or fractures) or family history. Some types can be diagnosed prenatally, whereas others only become apparent at birth or in early childhood. Screening for osteogenesis imperfecta on clinical grounds is sometimes initiated as part of the assessment of unexpected fractures in infants and young children, with confirmation by genetic testing. Genetic testing of children with an initial diagnosis of non-accidental injury or abuse identified 11 out of 262 children with collagen abnormalities in a retrospective analysis, 6 of whom were suspected to have osteogenesis imperfecta by referring physicians[136].

Clinical examination and review of radiographs of long bones and the skull, as well as evaluation of dentition provide the bases for clinical diagnosis. Signs of a generalized connective tissue disorder (such as short stature, relative macrocephaly, blue sclerae, characteristic facial or thoracic configuration, hearing loss, scoliosis and sarcopenia) are variable, but are taken into account. Depending on the setting, the diagnosis can be confirmed by genetic tests.

Use of next-generation sequencing approaches with panels of all known genes associated with osteogenesis imperfecta facilitates rapid diagnosis. If mutations of uncertain function are detected, gel electrophoretic analysis of collagen produced by cultured dermal fibroblasts from postnatal skin biopsies can be used to establish function; for example, biochemical analysis can detect alteration in the amount, structure or post-translational modification of type I procollagen in osteogenesis imperfecta type I (relatively reduced type I versus type III collagen levels), most cases of types II, III, IV, VII and VIII (collagen overmodification), as well as type XIV (undermodification). In rare instances when gene sequencing does not identify a mutation, a single or multi-exon deletion in *COL1A1* and *COL1A2* can be detected by multiplex ligation-dependent probe amplification or by marked overmodification of the chains of type I procollagen[137].

Screening

Routine screening for osteogenesis imperfecta is generally limited to prenatal ultrasonography imaging (FIG. 5), which can detect the perinatally lethal forms of osteogenesis imperfecta by 14–16 weeks of gestation, even in the absence of family history of the disease. Type III can be identified by ~18 weeks of gestation when longitudinal growth falls too close to the 5th percentile. Although this has not been reported, in principle, severe recessive cases should be detectable prenatally by ultrasonography. Sequencing of chorionic villus samples is sometimes used prenatally to confirm osteogenesis imperfecta in individuals with a family history of the disease.

Identification of a fetus with severe limb shortening and fractures provides information for potential early pregnancy termination after genetic confirmation or delivery management. Preimplantation genetic diagnosis is available for families in which a parent has a dominantly inherited form of osteogenesis imperfecta,

Box 3 | **Rehabilitation strategies and modalities in osteogenesis imperfecta**

- Targeted joint stretching and muscle strengthening programmes
- Weight-bearing activities and the use of ambulation aids (such as a walker, crutches or a cane) as required according to the amount of lower extremity strength[162]
- Lower extremity orthotics (such as splints and braces) to compensate for joint laxity or muscle weakness[162,241]
- Protective handling by the caregiver and positioning to avoid injuries and prevent contractures[152]
- Mobility devices such as manual or powered wheelchairs for specific environments
- Adaptive equipment to compensate for short stature, deformities and weakness[152]
- Environmental adaptations to the home, school or workplace to promote independence
- Physical fitness and healthy lifestyle coaching

for parents who are each carriers of a recessive form, and for families in whom parental mosaicism for a dominant form has been identified in one parent (usually because of parental testing after the identification of an affected fetus or infant in which genetic studies identified the causative gene and mutation). For those families, embryos that result from *in vitro* fertilization can be screened, and those not at risk to develop the disorder can be selected. Use of eggs or sperm from an unaffected individual can be used to assure that parental osteogenesis imperfecta is not transmitted.

Management

No cure exists for osteogenesis imperfecta. Management is symptom-based and depends on the type and severity of complications.

Musculoskeletal interventions

The wide clinical range of osteogenesis imperfecta, from severe short stature and bony deformities to very mild forms without fractures, leads to specific musculoskeletal challenges (BOX 1; TABLE 1). Features such as long bone bowing, joint laxity, and decreased range of motion and muscle strength can lead to delayed motor milestones, reduced mobility and limitations in activities of daily living[138–140].

Musculoskeletal impairments are greater in individuals with more-severe phenotypes[141] (TABLE 1). Individuals with osteogenesis imperfecta type I are community ambulators, who might exhibit limitations in sports and physical function[142,143]. Muscle strength, although difficult to measure in people who are fearful of fractures, has been reported as being reduced in those with osteogenesis imperfecta type I[142,144]. By contrast, individuals with osteogenesis imperfecta type III are exercise ambulators, with limitations in a protected rehabilitation environment, whose severe upper extremity deformities affect self-care and mobility[139,145,146]. Grip force was weaker in a sample of children with different types of osteogenesis imperfecta than in unaffected children[147], although the relative contributions of decreased muscle mass versus limited physical activity are unclear.

Musculoskeletal management of osteogenesis imperfecta consists of rehabilitation (pre-surgery and post-surgery), surgical interventions and medical treatment.

Rehabilitation. Rehabilitation is an especially crucial component in the management of osteogenesis imperfecta. An intervention study that analysed a 12-week graded exercise programme showed some short-term improvement in muscle force, indicating the benefits of rehabilitation[148].

For severely affected infants, initial rehabilitation facilitates parental bonding, by teaching parents how to handle a fragile baby. Later, rehabilitation focuses on maximizing strength, function and independence, and recovery from surgical procedures. Rehabilitation interventions are most beneficial: in infancy and early childhood if motor delays emerge, when overprotection or fear of movement prevents skills acquisition, during periods of transition to a new environment, and following injury, fracture or surgery. Physical rehabilitation is also useful as a support to pharmacological treatments of bone strength. Those with good baseline motor function require less intervention, particularly patients with osteogenesis imperfecta type I[139,149–151].

BOX 3 outlines the specific rehabilitation modalities and strategies that are widely used. Strengthening and weight bearing via aquatic therapy are strongly advocated for individuals with osteogenesis imperfecta as the environment is safer[152,153]. New modalities to increase bone density, such as weight bearing, as well as Pilates classes to increase core muscle strength, are emerging[154].

Orthopaedic management. The surgical management of osteogenesis imperfecta includes lower extremity, upper extremity and spine surgery, and is usually combined with medical treatment and pre-surgery and post-surgery rehabilitation.

Realignment with osteotomies (a surgical procedure in which a bone is cut to straighten it) with intramedullary rodding (insertion of a metal rod into the medullary cavity of a bone to provide strength and alignment) remains the best surgical option for lower extremity surgery in patients with osteogenesis imperfecta[155] (FIG. 6). Plates and screws should not be used, because stress might increase the risk of fracture above or below the plate[156]. Complications of rodding include migration of the nail outside the bone into soft tissue or joint space. Surgery on a child with bowed extremities should be performed when the child is ready to stand and walk. The use of telescoping rods (a compound rod with two segments that telescope into each other, are fixed by screws into bone at both ends and extend during growth) versus regular rods remains controversial, and is technically more demanding and expensive than straight rods[157]. The reoperation rate with telescoping rods is close to 50% compared with 58–87% with regular rods, but this number includes repeated surgery due to fractures or bent nails[158]. In addition, telescoping rods pose the risks of not elongating or of impacting the growth plate[159]. The choice of 'open' osteotomy or percutaneous osteotomy using a minimally invasive approach depends on the severity of the deformity and on the shape of the bone. Bilateral femurs and tibiae can be operated on in one surgical session, although a blood transfusion is likely to be necessary. Postoperative immobilization

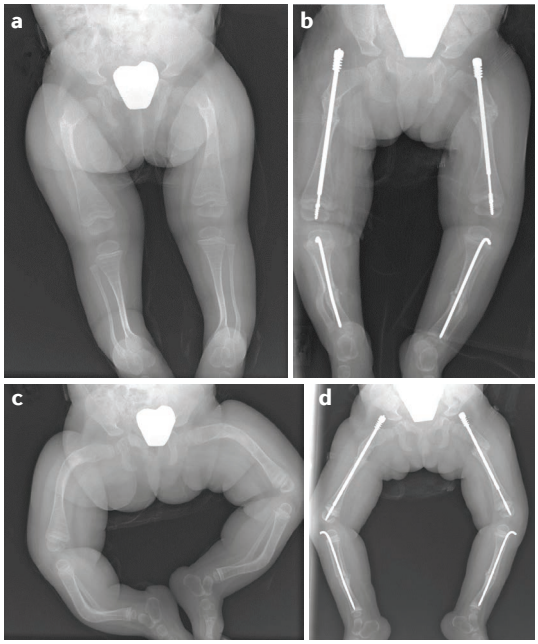

Figure 6 | **Lower extremity surgery in patients with osteogenesis imperfecta.** Radiographic images showing severe curvature of the legs (part **a** and part **c**) in two patients with osteogenesis imperfecta, which was ameliorated by rodding of the long bones (part **b** and part **d**).

should not exceed the healing time of a normal bone. Bracing and rehabilitation must be planned between surgeons and therapists.

Upper extremity surgery is performed more frequently than in the past because upper extremity deformities are now understood to affect self-care, whereas they were previously considered as purely cosmetic. Indeed, medical treatment now enables patients to walk, for which they need upper extremity function, for example, to use walking aids. Rodding of the humerus is technically demanding because of the need to protect the radial nerve; either telescoping or regular rods are used[160]. For forearm deformities, elastic rods or Kirschner wires (metallic wires that are used to align bone segments) are the best implants. Osteogenesis imperfecta type V represents a special challenge, both because of the risk of postoperative hyperplastic callus and the difficulty of treating intra-articular bone deformities, such as radial head dislocation, hypertrophy of the mandibular coronoid process and extension deformity of the distal humerus[161].

The use of bisphosphonates and consequent increase in bone mass and relief of vertebral compressions now enables the use of pedicular screws (screws inserted in the posterior arch and the vertebral body) and clamps, which give stronger fixation with reduced need for postoperative immobilization than hooks[162]. Although bisphosphonates have not decreased the incidence or extent of scoliosis, modest slowing of curve development in severe osteogenesis imperfecta type III allows surgery to be performed at an older age[163]. Severe curvature of the spine needs to be reduced before surgery with a halo-traction device (with multiple pin fixation).

Pharmacological treatment

Bone strength depends on bone material properties (quality), bone mass (amount) and bone architecture (distribution). The disorganized, hypermineralized bone matrix in osteogenesis imperfecta is not directly altered by any currently available pharmacological therapy[133]. However, both anti-resorptive (for example, bisphosphonates) and anabolic (for example, growth hormone) therapies might improve bone mass. It is hypothesized that it might be beneficial to have more bone of the same (poor) material quality.

Clear evidence exists that bisphosphonates improve bone microarchitecture[164], bone mass[165], long bone bowing deformity[166], and restore vertebral size and shape[150] in osteogenesis imperfecta. Vertebral compression was reduced, and areal bone density increased by about 1.5 standard deviation (z-score) in the first treatment year in most paediatric placebo-controlled trials in osteogenesis imperfecta[167]. However, bisphosphonate treatment will not improve ligament laxity, which is a major contributor to scoliosis in osteogenesis imperfecta. In agreement with this, retrospective analyses of scoliosis in children with osteogenesis imperfecta who were treated with bisphosphonates showed no improvement in the incidence of scoliosis at maturity, even in patients who were treated before 5 years of age, compared with children who had received no bisphosphonates[165,168,169]. Children with osteogenesis imperfecta type III had modest reduction in the rate of scoliosis progression in the first 2–4 years of treatment, but, ultimate, the incidence rate was unchanged[163].

For long bone fractures, there is limited evidence for anti-fracture efficacy of bisphosphonates in randomized controlled trials in children with osteogenesis imperfecta, and none in adults[170]. Meta-analyses and two Cochrane reviews did not support an effect of bisphosphonate treatment on long bone fractures in children with osteogenesis imperfecta[167,171,172]. This finding suggests that improving bone architecture may not be sufficient to overcome the increased fracture risk owing to altered bone material properties, particularly in more-severely affected children. In fact, treatment with bisphosphonates increased bone brittleness in mouse models at the whole-bone level, perhaps by impairing microcrack repair and decreased mineralization heterogeneity due to reduced bone turnover[173]. In addition, concerns have also arisen over the long cumulative half-life of bisphosphonates, which are incorporated in the bone matrix, and their possible contribution to impaired healing of fractures and osteotomies, and delayed tooth eruption. Furthermore, placebo-controlled trials did not confirm earlier case reports that bisphosphonate treatment reduced bone pain[167]. This finding might reflect a placebo effect in the case studies or might be owing to the lack of a disease-specific assessment tool.

Although bisphosphonates are widely regarded as part of multidisciplinary management in children with osteogenesis imperfecta, the consensus on which drug to use, in what dose or for how long is lacking. The maximum benefit based on the assessment of bone histology[174] and areal bone mineral density[175] occurs after ~3 years of treatment, but many children are treated continuously

until closure of the epiphyseal growth plates outside of research protocols. In addition, in contrast to adult studies of bisphosphonates in various diseases, reports of adverse events are few, but no systematic reporting is in place for comorbidities, and few long-term follow-up data are available.

Extraskeletal manifestations

Although skeletal findings predominate in osteogenesis imperfecta, other affected tissues include pulmonary and cardiac systems, vasculature and dentition[176]. Abnormalities in these systems should be monitored and treated according to organ-specific guidelines.

Pulmonary manifestations. Pulmonary complications are the leading cause of death in osteogenesis imperfecta and have been attributed to secondary effects of scoliosis and rib fractures[177–179]. Patients with osteogenesis imperfecta who have marked scoliosis can develop obstructive pulmonary disease and show progressive decline in pulmonary function parameters. Thus, patients with or who are suspected to have vertebral or chest wall deformities should be evaluated by spirometry (an analysis of pulmonary function) at a minimum and be further evaluated for standard pulmonary interventions. If restrictive or obstructive disease is identified, patients should be managed according to organ-specific guidelines. Recent evidence suggests that pulmonary function diminishes in osteogenesis imperfecta with age and lung disease is observed in individuals without scoliosis, suggesting that the lung defect might be intrinsic to the disease and not just the consequence of scoliosis[178,180].

Cardiovascular manifestations. Type I collagen is a major component of the extracellular matrix of cardiac valves and the aortic wall. Thus, altered type I collagen synthesis can affect their biomechanical properties[181], leading, in rare cases, to aortic dissection[182]. Most commonly reported cardiac abnormalities are aortic root dilation[183] and left-sided valvular regurgitation, and, occasionally, right-sided valve pathologies[184–186]. Echocardiography should be performed in patients with scoliosis or chest wall deformity, heart murmurs, or any cardiac or pulmonary symptomology with referral to appropriate specialists.

Bleeding diathesis. Tissue fragility and/or a bleeding diathesis (an unusual susceptibility to bleeding) owing to vessel fragility and platelet dysfunction have been reported in osteogenesis imperfecta[187]. As a consequence, patients with osteogenesis imperfecta can develop subdural and epidural haematomas after minimal trauma and have a higher risk of surgical complications[188,189].

Hearing loss. Half of patients with osteogenesis imperfecta develop hearing loss, usually between the second and fourth decades of life[190,191]. Conductive deafness is frequently associated with bony changes that affect the oval window region and lead to stapes footplate fixation due to thinning, atrophy and fractures of the stapes and the incus[192]. Initial conductive hearing loss can evolve into a mixed (conductive and sensorineural) hearing loss[193]. All patients with osteogenesis imperfecta should be evaluated for hearing loss on a regular basis, starting in childhood, and referred for hearing aids, stapes surgery or cochlear implants as needed.

Dental manifestations. Dentinogenesis imperfecta type I, a developmental disturbance of the dentin originating during tooth development, is associated with osteogenesis imperfecta caused by collagen structural defects[194] (FIG. 1b). Teeth with dentinogenesis imperfecta have a variable greyish-to-yellow-brown discolouration owing to the defective abnormal dentin shining through the translucent enamel. Owing to poorly mineralized dentin, enamel frequently fractures, which leads to rapid wear of the teeth even down to the gingiva[195]. Oral health treatment includes meticulous oral hygiene and approaches that focus on preventing caries and periodontal disease, and optimize aesthetics.

Adult management

Similar to other childhood-onset disorders, adults with osteogenesis imperfecta must transition their paediatric team care to individual adult providers who may not have the same levels of expertise in the condition[196,197]. Affected individuals should maintain routine health surveillance based on family health history risk stratification[198], and follow established screening guidelines for adult-onset disorders (http://www.uspreventiveservicestaskforce.org). As the prevalence of osteogenesis imperfecta in adults is low, no disease-specific treatment for the complications is currently available.

Because of the ongoing risk of fractures[199,200], it is important that patients have established relationships with adult orthopaedic surgeons who are familiar with osteogenesis imperfecta. Similar to patients with osteoporosis, adequate intake of calcium, maintenance of appropriate vitamin D levels and continued mobility are simple adjuncts to other medical interventions[201,202]. Pharmacological treatment should be individualized for each patient based on the type of osteogenesis imperfecta, the incidence of fractures, the degree of osteoporosis based on imaging studies, and the absence or presence of menopause[200,203]. Joint replacement might be required, and is most successful with custom joints based on detailed imaging compared with standard-shaped joints. The development of progressive scoliosis might lead to pulmonary complications and, in rare cases, the need for ventilation. Baseline and follow-up with pulmonary function tests should be performed on all adults with osteogenesis imperfecta[178,180].

Adults with osteogenesis imperfecta have an increased risk of aneurysms and dissections[182,183], and deafness compared with age-matched controls. Cardiac evaluation is important in individuals with severe progressive deforming osteogenesis imperfecta or with any cardiopulmonary symptoms[185]. Ongoing hearing assessments are also warranted to assess the need for hearing aids or cochlear implants[193]. In addition, problems related to dentinogenesis can have a great effect on quality of life (QOL)[204]. Skeletal pain is a frequent symptom in adults with osteogenesis imperfecta and should be treated in

a multidisciplinary approach, including orthopaedics, physiotherapists, psychologists and pain specialists. Other medical complications with increased occurrence in osteogenesis imperfecta include headaches associated with basilar invagination, glaucoma, renal manifestations, and the adverse effects of menopause on bone and overall health[205–208].

Quality of life

The clinical features of osteogenesis imperfecta and the associated treatments affect health, functioning and QOL. The WHO defines QOL as the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns[209]. With the exception of the physical functioning component of QOL, individuals with osteogenesis imperfecta report the same or better QOL (mental and psychosocial domains) compared with the general population[210,211]. Pain, fractures, scoliosis, activity limitations and participation restrictions due to decreased function are associated with lower levels of physical QOL[148,210–212]. For those with pulmonary problems, life expectancy may be affected. Not surprisingly, physical QOL is reported as worse by children with more-severe osteogenesis imperfecta than by children who are mildly affected[213]. Decreased physical functioning and environmental barriers impede QOL, suggesting that adaptation and accessibility may have a positive impact. The effect of bisphosphonate treatment on QOL is unclear as controlled trials to date used different definitions and measures[214–216]. Anecdotal reports support a slight improvement in overall QOL owing to bisphosphonate treatment.

QOL of caregivers of children with osteogenesis imperfecta is lower than the general population, particularly in the environmental domain, which incorporates the physical environment, accessibility to health and social care and opportunities for participation in leisure activities[217]. This domain also differed significantly between parents of children with mild versus severe osteogenesis imperfecta. Another study using the same measure found no differences with population norms, but also reported lower scores in the environmental domain among parents of children with severe compared with mild osteogenesis imperfecta[218].

A disease-specific QOL measure is under development, reflecting how parents, children and professionals working with osteogenesis imperfecta perceive the impact of this condition on QOL[219]. It will include six themes: being safe (avoiding impracticable activities), functioning, pain, fear of fracture, isolation and independence.

Outlook

Diagnosis and genetics

Prenatal sonography imaging does not always differentiate osteogenesis imperfecta from hypophosphatasia (a rare genetic metabolic bone disease) and other skeletal diseases. The increasing availability of genetic panels for skeletal dysplasia and the use of whole-exome sequencing will increase the number of patients with genetically confirmed osteogenesis imperfecta. However, prenatal diagnosis will cause enormous ethical considerations for parents and physicians, increasing the importance of interpretation of the results[220]. Genetic analysis facilitates accurate counselling for recurrence, but the genotype–phenotype correlation is currently not sufficiently strong to counsel families regarding the prognosis of the individual child[34,61,220].

Management of adults

After puberty, aspects of osteogenesis imperfecta other than bone fractures gain more importance. In adolescents and young adults, psychological problems owing to disability and impaired mobility, in addition to fears regarding their ability to lead an independent adult life, as well as financial and personal perspectives can cause symptoms of depression[221]. These problems are not exclusive to osteogenesis imperfecta and should be treated by psychologists who are experienced in treating patients with chronic diseases.

Because of the improved therapy of children with moderate and severe types of osteogenesis imperfecta, the life expectancy of patients may be extended. In a 2016 Danish study that included all individuals with osteogenesis imperfecta in a national registry but excluded prenatally or perinatally lethal types, the all-cause mortality rate among patients was nearly threefold that of the reference population, and life expectancy was reduced by 7–10 years overall in individuals with osteogenesis imperfecta, with approximately one-quarter of deaths occurring before 35 years of age[7]. Even severely affected patients reach an age at which other conditions that are not primarily related to osteogenesis imperfecta become more prevalent, such as malignancies. Treatment of these diseases in patients with severe osteogenesis imperfecta will be a challenge, requiring re-evaluation of standard therapeutic procedures. For example, very limited knowledge exists of the relative osteogenesis imperfecta-related and non-disease-related contributions to heart diseases, how to treat these patients[222,223] and whether modern therapeutic procedures are feasible[224]. The positive results reached in the paediatric field by treating patients in multidisciplinary teams should encourage all physicians to develop differentiated therapeutic strategies to also improve the situation for adults with osteogenesis imperfecta.

Emerging therapeutics

New pharmacological strategies are emerging that offer novel ways to address the fragility phenotype inherent to osteogenesis imperfecta. Increased TGFβ signalling has been observed in osteoblasts of patients[225] and in mouse models of osteogenesis imperfecta[31,226]; it is not yet clear to what extent the detected increase is a bystander effect. TGFβ-neutralizing antibodies can improve trabecular bone mass, cortical thickness and bone strength in *Crtap*$^{-/-}$ mice through combined reductions in both osteoclast and osteoblast activity. In addition, inhibition of the TGFβ pathway improves lung ultrastructure in this model[226]. Similar trabecular results were observed in *Col1a2*$^{+/p.G610C}$ (Amish) mice, suggesting that excessive TGFβ signalling might have a role in dominant and recessive models of osteogenesis imperfecta[226].

Anti-sclerostin therapy[227] might have a role in osteogenesis imperfecta management by promoting osteoblast recruitment and activity (FIG. 4a), provided that osteoblasts with collagen or collagen-related defects produce sufficient bone mass to overcome matrix level deficiencies in bone quality. Anti-sclerostin treatment for 2 weeks in 8-week-old Brtl/+ mice led to increased bone formation compared with placebo treatment[228]. To understand the efficacy of this approach during periods of rapid growth, Brtl/+ mice were treated from 3 weeks of age for 5 weeks — a period in which Brtl/+ mice more than doubles their body mass[229]. Compared with vehicle treatment, cortical thickness increased as a result of increased bone formation and reduced bone resorption[229]. Similar improvements in cortical and trabecular bone were observed in *Col1a2*$^{+/p.G610C}$ mice treated at 6 weeks of age, and in recessive *Crtap*$^{-/-}$ mice treated at 1 week or 6 weeks of age[230]. The cortical bone gains in young Brtl/+, *Col1a2*$^{+/p.G610C}$ and *Crtap*$^{-/-}$ mice translated into significant improvements in pre-yield measures of bone strength and stiffness[228–230]. Although post-yield bone brittleness remained unchanged, Raman spectroscopic analyses of bone of age-matched controls suggest that anti-sclerostin treatment may alleviate the high mineral to matrix ratio in newly formed bone tissue.

However, osteogenesis imperfecta is highly heterogeneous, and the underlying severity may influence the response to anti-sclerostin therapy. Although 4-week-old *Col1a1*$^{Jrt/+}$ mice, carrying an exon 9 splice donor site defect in one allele, showed 60% increase in distal femoral trabecular bone mass and nearly 20% increase in cortical thickness when treated for 4 weeks with a distinct, but similar, anti-sclerostin antibody as described above, the treatment did not translate to a structural benefit in the lumbar vertebrae or to a biomechanical benefit in the long bone, and 5-month-old mice showed no structural or biomechanical benefit at these sites[231]. Importantly, anti-sclerostin treatment will probably require sequential anti-resorptive intervention to preserve trabecular gains following cessation of anabolic therapy, although at levels that are lower than those used for primary intervention[232].

Molecular and cell therapy

Osteogenesis imperfecta is a genetic disease and its definitive cure will require the correction of the DNA defect. However, for classic osteogenesis imperfecta due to structural defects in *COL1A1* and *COL1A2* (BOX 1), specific suppression of the mutant *COL1A1* or *COL1A2* allele would convert the severe phenotype, owing to the dominant negative structural defect in collagen, to the milder form associated with the presence of a reduced amount (about half of normal) of collagen with normal structure[233]. Gene therapy approaches, using various silencing techniques (that is, ribozymes, small interfering RNA and short hairpin RNA), have been attempted *in vitro* and await final proof of principle *in vivo*[234]. Cell therapy using normal transplanted multipotent cells has also been attempted in preclinical and clinical trials, but cell engraftment was low[235]. Studies reported improved bone mechanics in mice receiving wild-type human fetal chorionic stem cells[236]. There remains a need to determine the best cell type and the optimum transplant timing to obtain higher engraftment in the bone compartment[237]. A clinical trial is approved in Europe to investigate the safety and effect on bone metabolism of fetal mesenchymal stem cells to enhance the production of normal collagen in children and fetuses with osteogenesis imperfecta. Cells will be given during the first months after birth or already *in utero* depending on the time of diagnosis (BOOSTB4; European Union Project ID: 681045)[238].

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