Recent Developments in Osteogenesis Imperfecta

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Recent developments in osteogenesis imperfecta [version 1; referees: 3 approved]

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Abstract
Osteogenesis imperfecta (OI) is an uncommon genetic bone disease associated with brittle bones and fractures in children and adults. Although OI is most commonly associated with mutations of the genes for type I collagen, many other genes (some associated with type I collagen processing) have now been identified. The genetics of OI and advances in our understanding of the biomechanical properties of OI bone are reviewed in this article. Treatment includes physiotherapy, fall prevention, and sometimes orthopedic procedures. In this brief review, we will also discuss current understanding of pharmacologic therapies for treatment of OI.

This article is included in the F1000 Faculty Reviews channel.
Introduction

Osteogenesis imperfecta (OI) is an unusual heritable disease that occurs in about 1 in 10,000 to 20,000 live births. The major clinical manifestation is skeletal fragility. Skeletal deformity, joint laxity, and scoliosis may be present. Other extraskeletal manifestations include hearing loss, dentinogenesis imperfecta, blue/gray sclerae, hypercalcruica, aortic root dilatation, and neurologic conditions such as macrocephaly, hydrocephalus, and basilar invagination. The phenotype is variable, ranging from osteoporosis presenting in adulthood to lethality in children. Even adults with “mild” OI may have significant musculoskeletal symptoms, including arthritis, fractures, back pain, scoliosis, and tendon ruptures.

About 90% of patients have mutations in type I collagen genes (COL1A1 and COL1A2); however, many other genes have now been described. Some of the genes encode proteins related to type I collagen (for example, enzymes that modify type I collagen, chaperone proteins, and signaling proteins). In 1979, Sillence et al. proposed a classification system for OI with four types based on severity: type I mild non-deforming, type II perinatal lethal, type III severely deforming, and type IV moderately deforming. This classification has been expanded as new genes were discovered. Phenotypic classification (types I to V with multiple genes included in some of the types) has been proposed. Alternatively, classification by genetics has been proposed (see Table 1), which was created through modifications of references.

There have been recent advances in the understanding of the structure and mechanical properties of bone in children with OI. These advances may lead to improved finite element (FE) models that help predict fracture risk of specific activities and help plan physiotherapy.

In addition to physiotherapy and orthopedic surgery when needed, intravenous bisphosphonates have been used extensively in moderate to severe OI in childhood. Less is known about pharmacologic treatment in adults. Anabolic therapy with PTH 1-34 has been studied in adults with OI. Future therapies may include antibodies to sclerostin, transforming growth factor beta (TGFβ) antagonism, gene therapy, and cell-based therapies.

Genes and classification

OI is most commonly caused by mutations in type I collagen. Type I collagen is a rod-like structure formed from a trimer of 2 COL1A1 and 1 COL1A2 subunits, which requires post-translational modification. Many of the other rare forms of OI are due to defects in different genes.

Table 1. Classification of osteogenesis imperfecta.

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Protein</th>
<th>Defect</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AD</td>
<td>COLA1/COLA2</td>
<td>α1(1) collagen</td>
<td>Collagen quantity</td>
<td>Mild, non-deforming</td>
</tr>
<tr>
<td>II</td>
<td>AD</td>
<td>COLA1/COLA2</td>
<td>α1(1)/α2(1) collagen</td>
<td>Collagen structure</td>
<td>Perinatal lethal</td>
</tr>
<tr>
<td>III</td>
<td>AD</td>
<td>COLA1/COLA2</td>
<td>α1(1)/α2(1) collagen</td>
<td>Collagen structure</td>
<td>Progressively deforming</td>
</tr>
<tr>
<td>IV</td>
<td>AD</td>
<td>COLA1/COLA2</td>
<td>α1(1)/α2(1) collagen</td>
<td>Collagen structure</td>
<td>Moderately deforming</td>
</tr>
<tr>
<td>V</td>
<td>AD</td>
<td>IFITM5</td>
<td>BRIL</td>
<td>Matrix mineralization</td>
<td>Moderate, distinct histology</td>
</tr>
<tr>
<td>VI</td>
<td>AR</td>
<td>SERPINF1</td>
<td>PEDF</td>
<td></td>
<td>Moderate to severe, distinct histology</td>
</tr>
<tr>
<td>VII</td>
<td>AR</td>
<td>CRTAP</td>
<td>CRTAP</td>
<td>Prolyl 3 hydroxylation</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>VIII</td>
<td>AR</td>
<td>LEPRE1</td>
<td>P3H1</td>
<td>Prolyl 3 hydroxylation</td>
<td>Severe to lethal</td>
</tr>
<tr>
<td>IX</td>
<td>AR</td>
<td>PPIB</td>
<td>CyPB</td>
<td>Prolyl 3 hydroxylation</td>
<td>Moderate to lethal</td>
</tr>
<tr>
<td>X</td>
<td>AR</td>
<td>SERPINF1</td>
<td>HSP47</td>
<td>Collagen chaperoning</td>
<td>Severe</td>
</tr>
<tr>
<td>XI</td>
<td>AR</td>
<td>FKBP10</td>
<td>FKBP65</td>
<td>Telopeptide hydroxylation</td>
<td>Progressively deforming (Bruck syndrome)</td>
</tr>
<tr>
<td>XII</td>
<td>AR</td>
<td>SP7</td>
<td>SP7/osterix</td>
<td>Osteoblast development</td>
<td>Moderate</td>
</tr>
<tr>
<td>XIII</td>
<td>AR</td>
<td>BMP1</td>
<td>BMP1/mTLD</td>
<td>Collagen processing</td>
<td>Severe, high bone mass</td>
</tr>
<tr>
<td>XIV</td>
<td>AR</td>
<td>TMEM38B</td>
<td>TRIC-B</td>
<td>Cation channel defect</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>XV</td>
<td>AR</td>
<td>WNT1</td>
<td>WNT1</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>XV</td>
<td>AD</td>
<td>WNT1</td>
<td>WNT1</td>
<td>Early-onset osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

Others

| AD | CREB3L1 | Oasis | COL1A1 transcription | Progressively deforming |
| XL | PLS3    | Plasmin | Osteocyte defect | Mild |
| AR | PLOD2   | Lysyl hydroxylase 2 | Collagen telopeptide hydroxylation | Progressively deforming |

AD, autosomal dominant; AR, autosomal recessive; XL, x-linked.
proteins involved in cross-linking, hydroxylation, and mineralization of type I collagen.

Mutations of CRTAP, which encodes cartilage-associated protein, have been shown to cause recessive OI.\textsuperscript{11-13} Mutations of LEPRE1, which encodes prolyl 3 hydroxylase\textsuperscript{14-16}, and PPILB (protein cyclophillin B)\textsuperscript{17-18} also cause recessive OI. The proteins described above form a complex that modifies specific prolines in the collagen and these mutations result in moderate to lethal OI.

\textbf{SERPINI1} mutations cause severe recessive OI\textsuperscript{20}. The protein affected in \textit{SERPINI1} mutations, HSP47, is a collagen chaperone protein\textsuperscript{4}. \textit{FKBP10} mutations cause recessive OI (progressively deforming)\textsuperscript{21}. This gene encodes the protein FKBP65, which appears to be needed for hydroxylation of collagen telopeptide lysine\textsuperscript{22}. Both HSP47 and FKBP65 are needed for the proper folding of the collagen triple helix. Furthermore, Bruck syndrome (OI and congenital contractures) can be caused by homozygous mutations on \textit{FKBP10}\textsuperscript{10,23}, and Kuskokwim syndrome (congenital contractures with mild skeletal problems seen in Yup’ik people in Alaska) is caused by \textit{FKBP10} mutations\textsuperscript{24}. \textit{PLOD2} mutations also cause recessive OI\textsuperscript{25}. \textit{PLOD-2} encodes lysyl hydroxylase 2, which hydroxylates collagen telopeptide lysine. Bruck syndrome can also be caused by homozygous mutations of \textit{PLOD2}\textsuperscript{25}.

\textit{BMP1} (bone morphogenetic protein 1) mutations also cause recessive OI\textsuperscript{16,27}. The protein, BMP1, is a protease that cleaves the c-propeptide of type I collagen\textsuperscript{27}, but also has other substrates. \textit{SP7} mutations cause recessive OI\textsuperscript{12}. \textit{SP7} encodes the protein osterix, which may be needed for osteoblast differentiation\textsuperscript{10}. \textit{WNT1} mutations\textsuperscript{28-30} have been reported in early-onset osteoporosis (dominant) and OI (recessive). The protein, WNT1, may be important in the beta catenin system, which stimulates bone formation\textsuperscript{29-31}.

\textit{TMEM38B} mutations have been reported in recessive OI\textsuperscript{32}. This gene encodes TRIC-B, which may be important in intracellular calcium signaling. Defective TRIC-B may cause bone disease through defective calcium signaling in bone cells\textsuperscript{30}. \textit{CREB3L1} mutations cause recessive OI\textsuperscript{11}. \textit{CREB3L1} encodes the protein OASIS, which may activate transcription of \textit{COL1A1}\textsuperscript{14}. \textit{PLS3} (plasin 3) mutations have been reported in x-linked osteoporosis\textsuperscript{3-37}. Plasin 3 is expressed in osteocyte dendrites and may be important in mechanosensing\textsuperscript{38}. Bone biopsies from patients with \textit{PLS3} mutations have shown cortical and trabecular osteoporosis with normal to low bone formation rates\textsuperscript{36,37}. There is no mineralization defect\textsuperscript{36,37}.

Mutations in \textit{IFITM5}, a bone-restricted IFITM-like protein (BRIL) (dominant) cause type V OI\textsuperscript{16-42}. These patients have prominent calcius formation and ossification of the forearm interosseous membrane\textsuperscript{38-42}. They also have mesh-like lamellation on bone biopsy as well as a mineralization defect\textsuperscript{38-42}. There appear to be substantial differences in phenotypic presentation even with similar mutations\textsuperscript{39-42}. Type VI OI is caused by mutations in \textit{SERPINF1} (protein PEDF)\textsuperscript{13,44}. Children with type VI OI have elevated alkaline phosphatase, and bone biopsy reveals fish-scale pattern under polarized light as well as broad bands of unmineralized osteoid\textsuperscript{13,44}. Interestingly, some patients with BRIL mutations have phenotypic type VI OI (rather than type V)\textsuperscript{45}. BRIL and PEDF are related, and it appears that mutations causing gain-of-function of BRIL cause OI type V and that those causing loss-of-function of BRIL look phenotypically like OI type VI\textsuperscript{45}.

\textbf{Structure and mechanical properties of bones in osteogenesis imperfecta}

From a mechanical perspective, increased fracture risk in individuals with OI could stem from a combination of reduced bone mass, decreased bone material quality, and, in some individuals, the presence of bone deformity.

\textbf{Bone mass}

Low bone mass is a clinical characteristic of OI, and individuals with this disorder tend to have markedly reduced areal bone mineral density (BMD)\textsuperscript{47-49}. This reduced bone mass can be the consequence of decreased bone size or decreased volumetric BMD or both\textsuperscript{49,50}. Studies of iliac crest biopsies have revealed lower bone tissue quantity in children with moderate and severe OI, including reduced bone volume fraction, and decreased trabecular and cortical thicknesses\textsuperscript{51-53}. Decreased bone volume, though less marked, was also noted in some children with mild OI\textsuperscript{52}.

In cortical bone specimens from the long bone shafts of children with OI, “atypical, flattened, and large resorption lacunae”\textsuperscript{54} and abnormally elevated porosity have been observed\textsuperscript{55,57}. For example, an average intracortical vascular porosity of 21% was found in bone shaft osteotomies from children with OI by synchrotron radiation micro-computed tomography\textsuperscript{53,57}; the corresponding value in normal pediatric bones was 3%\textsuperscript{57}. From a structural perspective, reduced bone mass can lead to increased stresses within the bone as a result of a smaller area of bone tissue present to support physiological loads. For this reason, low bone mass is likely a considerable contributor to bone fragility in OI.

\textbf{Bone material quality}

In addition to the structural deficiency (low bone mass), mechanical quality of the bone material in OI is reduced. The genetic defects causing OI affect type I collagen, the main organic component of bone. As discussed earlier, most forms of OI (types I to IV) are attributed to insufficient collagen production or amino acid substitution defects within the collagen molecules or both\textsuperscript{56-63}, and less common recessive forms have been associated with abnormalities in other proteins that interact with type I collagen\textsuperscript{64}. Since type I collagen is an integral component of bone tissues, it should be no surprise that abnormalities affecting this protein would impact bone material quality. At the ultrastructural level, irregularities in collagen and mineral geometry as well as abnormalities in mineral composition have been reported\textsuperscript{65-70}. Studies in mice indicated that the material abnormalities in OI have a negative impact on bone material properties\textsuperscript{71-78}. A few studies have also used biopsy and osteotomy specimens to measure bone material properties in humans with this disorder. Some of these studies used nanoindentation, a technique in which a diamond-tip indenter is pressed into the polished surface of a material (in this case, bone), creating an indent a few microns in size. With this test, elastic modulus and hardness—that is, properties representing the material’s resistance to elastic (recoverable)
and plastic (non-recoverable) deformation, respectively—are determined at the submicrostructural level. Based on nanoindentation, slightly higher elastic modulus and hardness were found in children with mild (type I) versus severe (type III) OI\textsuperscript{79}, whereas these properties were not found to differ between children with severe (type III) versus moderately severe (type IV) phenotypes\textsuperscript{78}. However, exactly how these properties compare with normal tissues remains unclear; one study reported higher elastic modulus and hardness in children with severe OI versus controls\textsuperscript{79}, whereas another reported the opposite\textsuperscript{80}. Furthermore, bone tissues have a complex hierarchical structure, which results in properties that differ between length scales, and nanoindentation provides only limited insight regarding bone tissue properties at the submicrostructural scale. Another limitation with this technique is that it does not measure strength, a property representing the ability of a material to carry stress without breaking or sustaining damage.

Recent studies have measured cortical bone material properties, including strength, at a larger scale by using surgical bone specimens from long bone diaphyses of children with OI\textsuperscript{77,80,81}. In these studies, small osteotomy specimens were machined into parallelepiped-shaped specimens and loaded to failure in either bending\textsuperscript{56,81} or compression\textsuperscript{82}. Bone material strength was confirmed to be lower than normal in these children, and this property was found to be negatively related to an abnormally elevated intracortical porosity. These findings suggest that increased cortical porosity contributes to increased risk of long bone fractures in OI.

Bone deformity
In addition to decreased bone mass and reduced bone material quality (low bone material strength), deformities of the spine and long bones are common in OI. For example, children with severe OI often exhibit anterolateral bowing of the femur and anterior bowing of the tibia\textsuperscript{47}. Increased curvature in long bones leads to an increase in maximum stresses within the bone shaft\textsuperscript{82}. The increased stresses attributed to bone deformities in OI can further contribute to the risk of bone fracture.

Fracture prediction based on mechanical models
Mechanical modeling through the use of FE analysis is a well-established technique that allows detailed analysis of composite structures under a variety of load conditions. In the field of orthopedic biomechanics, FE modeling is frequently used to examine the responses of bone to loading\textsuperscript{18-46}. Patient-specific FE models have been effective for bone strain and fracture strength assessment, and as recently as 2009 Fritz et al. applied these models to predict fractures in OI\textsuperscript{12,78}. A femoral model including muscle forces was analyzed during all seven phases of the gait cycle and geometrically matched to bone anatomy with x-rays. The most current work includes advanced meshing techniques for improved geometric biofidelity and updated mechanical property data\textsuperscript{82}. Other FE models for assessing OI bones have also been reported. Orwoll et al. used FE modeling to estimate vertebral strength in a study of the effects of teriparatide treatment in adults with OI\textsuperscript{83}. Caouette et al. developed an FE model to assess fracture risk at the tibia in children with OI\textsuperscript{84}. This tibia model examined fracture risk during two-legged hopping, lateral loading, and torsional loading. Future applications of FE modeling may prove invaluable for better quantification of fracture risk in OI. These models could help identify activities that pose greater risk of fracture and, through appropriate controls, may enable persons with OI to participate safely and more fully in a greater spectrum of daily and recreational activities.

Management

Physical therapy
The goals of the treatment in OI are to decrease pain and fractures and to maximize mobility. Physical therapy/rehabilitation\textsuperscript{77} is particularly important in children to improve weight bearing and prevent fractures as well as to increase strength and mobility during fracture recovery. Some children may require wheelchairs or walking aids. Occupational therapy may be needed to help with daily living activities.

Pharmacologic therapy

Bisphosphonates
Bisphosphonates (BPs) are non-hydrolysable synthetic analogs of pyrophosphate\textsuperscript{92}. BPs adhere to mineralized surfaces, inhibit osteoclastic bone resorption, and have very long skeletal half-lives\textsuperscript{92}. Intravenous BPs are currently the primary treatment of children with moderate to severe OI. BPs increase BMD and size in children with OI\textsuperscript{93}. BPs do not appear to impair bone formation that increases cortical width in children with OI\textsuperscript{94}. Observational studies suggest decreased fractures\textsuperscript{94,95}, decreased bone pain, and improved vertebral shape\textsuperscript{94,95}. Ability to perform activities of daily living may also be improved. However, it has been difficult to confirm all of these benefits in randomized trials, and the optimal duration of BP treatment is unknown.

In a study of children with predominantly mild OI, oral risedronate increased BMD and appeared to decrease clinical fractures\textsuperscript{96}. Atypical fractures have been reported in children with OI treated with bisphosphonates\textsuperscript{97,98}; however, osteonecrosis of the jaw does not appear to be a major problem in children with OI treated with BPs\textsuperscript{99-101}. Several studies have been done on the use of intravenous or oral BPs in adults with OI. Although BMD increases have been reported during these treatments, fracture data are equivocal\textsuperscript{102-106}. A Cochrane review found increased BMD in patients with OI treated with BPs but did not find definitive evidence of fracture reduction\textsuperscript{107}. Furthermore, a recent meta-analysis of placebo-controlled trials suggested that the effects of BPs for fracture prevention in OI were inconclusive\textsuperscript{108}.

Growth hormone
Growth hormone has anabolic effects on bone. A 1-year randomized trial of the BP, neridronate, with or without growth hormone showed greater increase in BMD and growth velocity with growth hormone, but there was no fracture benefit of growth hormone\textsuperscript{109}.

Teriparatide
Teriparatide (PTH1-34) is an anabolic agent that stimulates bone formation (and ultimately bone resorption). This drug decreases vertebral and non-vertebral fractures in post-menopausal women.
with osteoporosis. Observational data in adults with OI suggest increased BMD with teriparatide. Recently, a randomized trial of teriparatide in adults with OI showed increased BMD as well as increased vertebral strength estimated by FE analysis. The benefits appeared to occur in mild (type I) OI but not in more severe OI (types III and IV).

Denosumab
Denosumab is a monoclonal antibody to receptor activator of nuclear factor kappa B ligand that decreases bone resorption, increases bone density, and reduces fractures in women with postmenopausal osteoporosis. This drug may represent a future therapy in OI. In a study of four children with type VI OI, increased BMD and mobility and improved vertebral shape were reported after denosumab treatment, and the outcomes of this study indicated that this treatment appears to be safe. There is also a report of denosumab use in two children with OI caused by COL1A1/A2 mutations. As with BPs, “zebra lines” were present, suggesting continued longitudinal growth. Denosumab has been reported to cause hypophosphatemia, hypocalcemia, and secondary hyperparathyroidism in a child with fibrous dysplasia of bone. There was rebound hypercalcaemia after stopping denosumab.

Possible future therapies
Sclerostin is an inhibitor of the LRPS/Wnt system that decreases osteoclastic bone resorption. Sclerostin antibody appeared to be effective in a mouse model of treatment of osteoporosis with the goal to increase bone density. There is also a report that this treatment appears to be safe. There is also a report of denosumab use in two children with OI caused by COL1A1/A2 mutations. As with BPs, “zebra lines” were present, suggesting continued longitudinal growth. Denosumab has been reported to cause hypophosphatemia, hypocalcemia, and secondary hyperparathyroidism in a child with fibrous dysplasia of bone. There was rebound hypercalcaemia after stopping denosumab.

Cell-based therapy, such as bone marrow or mesenchymal stem cell transplantation, has also been investigated and may have promise; but these could also have significant risks. Gene therapy with allele-specific silencing may represent a future therapy.

Summary
Although most cases of OI are caused by COL1A1/A2 mutations, many new genetic causes have been identified in recent years. Some of these genes are related to the processing of type I collagen. Furthermore, we have greater understanding of the biomechanics of OI bone, including material properties, muscle and gait load effects, and fracture strength assessment. Biomechanical models could help identify activities that pose greater risk of fracture and, through appropriate controls, may enable persons with OI to participate safely and more fully in a greater spectrum of activities. Physical therapy is an important part of the management of these patients. Intravenous BPs are commonly used in children with moderate to severe OI. Some of the benefits seen in observational studies have been hard to prove in controlled studies. Treatment of adults with OI is less well studied. BPs and teriparatide appear to increase BMD, but fracture data are lacking. Teriparatide appears to increase bone strength as estimated by FE analysis in adults with mild OI. Other promising treatments for OI are under investigation.

Competing interests
JS is a consultant for Alexion Pharmaceuticals. The other authors declare that they have no competing interests.

Grant information
The author(s) declared that no grants were involved in supporting this work.

References


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Open Peer Review

Current Referee Status: ✔️ ✔️ ✔️

Version 1

Referee Report 07 September 2015

doi:10.5256/f1000research.6864.r10219

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 07 September 2015

doi:10.5256/f1000research.6864.r10218

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 07 September 2015

doi:10.5256/f1000research.6864.r10217

Malachi McKenna
St. Vincent's University Hospital, Dublin, Ireland

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
I have noted a few issues in this article:

1. On page 2, in the section headed "Genes and classification", gene symbols (COL1A1 and COL1A2) are inappropriately used to designate the component protein chains of type I collagen. Gene symbols and protein product names should not be used interchangeably. The protein chains are α1(I) and α2(I) respectively.

2. In Table 1, the gene symbols for the mutant genes leading to OI types I, II, III and IV are incorrect. They should be COL1A1 and COL1A2, not COL1A1 and COLA2.

3. In Table 1, the gene symbol for the gene encoding the protein prolyl-3 hydroxylase is P3H1, not LEPRE1. The gene symbol for this gene was changed to P3H1 in December 2014.

4. Table 1 continues to propagate the notion that there are very many OI types when, in reality, there are really only five true types which can be clearly distinguished clinically (types I to V). The problem has been caused by several new OI types being created to correspond to newly discovered genes which harbour OI-causing sequence variants. This has only served to confuse matters and is discussed at length by Van Dijk and Sillence (2014) (http://www.ncbi.nlm.nih.gov/pubmed/24715559).

5. It is perhaps unsurprising that the article gives emphasis to pharmacological interventions for OI, given that one of the authors is employed by Alexion Pharmaceuticals, but it is improper to ignore surgical interventions such as rodding of long bones and mesenchymal stem cell therapy.

6. There is no mention in the article of the fact that there is a comprehensive database of gene variants leading to OI: https://oi.gene.le.ac.uk/.

7. The list of OI genes is incomplete in Table 1. A comprehensive list of genes may be found at https://oi.gene.le.ac.uk/status.php.

**Competing Interests:** I declare that I curate the database of OI gene variants which in mentioned in comment 6.