REVIEW

Recent developments in osteogenesis imperfecta [v1; ref status: indexed, http://f1000r.es/5ao]

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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.

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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, hypercalciuria, 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 other genes. The Table 1 provides a classification of OI based on the type of gene mutation.

Table 1. Classification of osteogenesis imperfecta.

| Type | Inheritance | Gene           | Protein              | Defect                     | Phenotype                        |
|------|-------------|----------------|----------------------|----------------------------|----------------------------------|
| I    | AD          | COL1A1/COLA2   | α1(1) collagen       | Collagen quantity          | Mild, non-deforming              |
| II   | AD          | COL1A1/COLA2   | α1(1)/α2(1) collagen | Collagen structure         | Perinatal lethal                 |
| III  | AD          | COL1A1/COLA2   | α1(1)/α2(1) collagen | Collagen structure         | Progressively deforming          |
| IV   | AD          | COL1A1/COLA2   | α1(1)/α2(1) collagen | Collagen structure         | Moderately deforming             |
| V    | AD          | IFITM5         | BRIL                 | Matrix mineralization      | Moderate, distinct histology     |
| VI   | AR          | SERPINF1       | PEDF                 |                            | Moderate to severe, distinct histology |
| VII  | AR          | CRTAP          | CRTAP                | Prolyl 3 hydroxylation     | Severe to lethal                 |
| VIII | AR          | LEPRE1         | P3H1                 | Prolyl 3 hydroxylation     | Severe to lethal                 |
| IX   | AR          | PP1B           | CyPB                 | Prolyl 3 hydroxylation     | Moderate to lethal               |
| X    | AR          | SERPIN1H1      | HSP47                | Collagen chaperoning       | Severe                           |
| XI   | AR          | FKBP10         | FKBP65               | Telopeptide hydroxylation  | Progressively deforming (Bruck syndrome) |
| XII  | AR          | SP7            | SP7/osterix          | Osteoblast development     | Moderate                         |
| XIII | AR          | BMP1           | BMP1/mTLD            | Collagen processing        | Severe, high bone mass           |
| XIV  | AR          | TMEM38B        | TRIC-B               | Cation channel defect      | Moderate to severe               |
| XV   | AR          | WNT1           | WNT1                 |                            | Variable                         |
| XV   | AD          | WNT1           | WNT1                 |                            | Early-onset osteoporosis         |

Others

| AR    | CREB3L1   | Oasis | COL1A1 transcription | Progressively deforming |
|-------|-----------|-------|----------------------|-------------------------|
| XL    | PLS3      | Plastin | 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 \textit{CRTAP}, which encodes cartilage-associated protein, have been shown to cause recessive OI\textsuperscript{11,12}. Mutations of \textit{LEPRE1}, which encodes prolyl 3 hydroxylase\textsuperscript{26,38}, and \textit{PPIB} (protein cyclophycin B)\textsuperscript{30,39} 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.

\textit{SERPINH1} mutations cause severe recessive OI\textsuperscript{20}. The protein affected in \textit{SERPINH1} mutations, HSP47, is a collagen chaperone protein\textsuperscript{41}. \textit{FKBP10} mutations cause recessive OI (progressively deforming)\textsuperscript{41}. 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{30,39}, and Kuskokwim syndrome (congenital contractures with mild skeletal problems seen in Yup’ik people in Alaska) is caused by \textit{FKBP10} mutations\textsuperscript{42}. \textit{PLOD2} mutations also cause recessive OI\textsuperscript{45}. \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{35}.

\textit{BMP1} (bone morphogenetic protein 1) mutations also cause recessive OI\textsuperscript{6,27}. This gene encodes BMP-1, a pro tease that cleaves the c-propeptide of type I collagen\textsuperscript{6,27} but also has other substrates. \textit{SP7} mutations cause recessive OI\textsuperscript{6,27}. \textit{SP7} encodes the protein osterix, which may be needed for osteoblast differentiation.\textsuperscript{10} \textit{WNT1} mutations\textsuperscript{20,31} 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{20,31}.

\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{32}. \textit{CREB3L1} mutations cause recessive OI\textsuperscript{13}. \textit{CREB3L1} encodes the protein OASIS, which may activate transcription of \textit{COL1A1}\textsuperscript{14}. \textit{PLS3} (plastin 3) mutations have been reported in x-linked osteoporosis (dominant) and OI (recessive). \textit{PLS3} mutations have caused 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 calciﬁcation and ossiﬁcation of the forearm interosseous membrane\textsuperscript{18,42}. They also have mesh-like lamellation on bone biopsy as well as a mineralization defect\textsuperscript{18,42}. There appear to be substantial differences in phenotypic presentation even with similar mutations\textsuperscript{20,42}. 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{46}.

\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{56,57}. 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{55,57}; the corresponding value in normal pediatric bones was 3%\textsuperscript{55}. 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{66–70}. Studies in mice indicated that the material abnormalities in OI have a negative impact on bone material properties\textsuperscript{71–76}. 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, whereas these properties were not found to differ between children with severe (type III) versus moderately severe (type IV) phenotypes. 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, whereas another reported the opposite. 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. In these studies, small osteotomy specimens were machined into parallelepiped-shaped specimens and loaded to failure in either bending or compression. 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. Increased curvature in long bones leads to an increase in maximum stresses within the bone shaft. 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. 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. 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. 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. Caouette et al. developed an FE model to assess fracture risk at the tibia in children with OI. 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 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. BPs adhere to mineralized surfaces, inhibit osteoclastic bone resorption, and have very long skeletal half-lives. Intravenous BPs are currently the primary treatment of children with moderate to severe OI. BP increases BMD and size in children with OI. BPs do not appear to impair bone formation that increases cortical width in children with OI. Observational studies suggest decreased fractures, decreased bone pain, and improved vertebral shape. 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 risdronate increased BMD and appeared to decrease clinical fractures. Atypical fractures have been reported in children with OI treated with bisphosphonates; however, osteonecrosis of the jaw does not appear to be a major problem in children with OI treated with BPs. 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. A Cochrane review found increased BMD in patients with OI treated with BPs but did not find definitive evidence of fracture reduction. Furthermore, a recent meta-analysis of placebo-controlled trials suggested that the effects of BPs for fracture prevention in OI were inconclusive.

**Growth hormone**

Growth hormone has anabolic effects on bone. A 1-year randomized trial of the BP, neriodronate, 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.

**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\textsuperscript{110}. Observational data in adults with OI suggest increased BMD with teriparatide\textsuperscript{107,111}. Recently, a randomized trial of teriparatide in adults with OI showed increased BMD as well as increased vertebral strength estimated by FE analysis\textsuperscript{112}. 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\textsuperscript{113}. 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\textsuperscript{114}. There is also a report of denosumab use in two children with OI caused by COL1A1/A2 mutations\textsuperscript{115}. As with BPs, “zebra lines” were present, suggesting continued longitudinal growth\textsuperscript{116}. Denosumab has been reported to cause hypophosphatemia, hypocalcemia, and secondary hyperparathyroidism in a child with fibrous dysplasia of bone\textsuperscript{117}. There was rebound hypercalcemia after stopping denosumab\textsuperscript{118}.

**Possible future therapies**

Sclerostin is an inhibitor of the LRP5/Wnt system that decreases bone formation. Antibodies to sclerostin are in clinical trials for treatment of osteoporosis with the goal to increase bone density and fracture strength as estimated by FE analysis in adults with mild OI\textsuperscript{119}. Other benefits appeared to occur in mild (type I) OI but not in more severe OI\textsuperscript{120}. TGF\(\beta\) is secreted by osteoblasts and increases osteoclastic bone resorption\textsuperscript{121}. Excessive TGF\(\beta\) signaling may be important in some forms of OI, and anti-TGF\(\beta\) therapy represents an interesting prospect for the future treatment of OI\textsuperscript{122}.

Cell-based therapy, such as bone marrow\textsuperscript{123} or mesenchymal stem cell\textsuperscript{124–126} 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\textsuperscript{127}.

**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.

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**References**

1. Monti E, Mottes M, Fraschini P, et al.: Current and emerging treatments for the management of osteogenesis imperfecta. Ther Clin Risk Manag. 2010; 6: 367–81. PubMed Abstract | Publisher Full Text | Free Full Text

2. Arponen H, Mäkikie O, Waltimo-Sirén J: Association between joint hypermobility, scoliosis, and cranial base anomalies in paediatric Osteogenesis imperfecta patients: a retrospective cross-sectional study. BMC Musculoskeletal Disorder. 2014; 15: 428. PubMed Abstract | Publisher Full Text | Free Full Text

3. Lindahl K, Langholt B, Ljunggren O, et al.: Treatment of osteogenesis imperfecta in adults. Eur J Endocrinol. 2014; 171(2): R79–90. PubMed Abstract | Publisher Full Text

4. Lamanna A, Fayers T, Clarke S, et al.: Null mutations in lepre1 cause imperfecta in the adult. J Med Genet. 2008; 45(3): 195–203. PubMed Abstract | Publisher Full Text

5. Bógh A, Munns CF: Osteogenesis imperfecta: diagnosis and treatment. Curr Osteoporos Rep. 2014; 12(3): 279–88. PubMed Abstract | Publisher Full Text

6. McKernan FE: Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. Osteoporos Int. 2005; 16(12): 1698–702. PubMed Abstract | Publisher Full Text | Free Full Text

7. Silteno DO, Senn A, Danks DM: Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979; 16(2): 101–16. PubMed Abstract | Publisher Full Text | Free Full Text

8. Valadares ER, Carneiro TB, Santos PM, et al.: What is new in genetics and osteogenesis imperfecta classification? J Pediatr (Rio J). 2014; 90(6): 536–41. PubMed Abstract | Publisher Full Text

9. Forlino A, Cabral WA, Barnes AM, et al.: New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol. 2011; 7(9): 540–57. PubMed Abstract | Publisher Full Text | Free Full Text

10. Marini JC, Reich A, Smith SM: Osteogenesis imperfecta due to mutations in non-collagenous genes: lessons in the biology of bone formation. Curr Opin Pediatr. 2014; 26(1): 506–7. PubMed Abstract | Publisher Full Text | Free Full Text

11. Barnes AM, Chang W, Morello R, et al.: Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. N Engl J Med. 2008; 359(26): 2757–64. PubMed Abstract | Publisher Full Text | Free Full Text

12. Morello R, Brinton TK, Chen Y, et al.: CRTAP is required for prolyl 3-hydroxylation and mutations cause recessive osteogenesis imperfecta. Cell. 2008; 132(2): 291–304. PubMed Abstract | Publisher Full Text | Free Full Text

13. Balsridge D, Schwarze U, Morello R, et al.: CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. Hum Mutat. 2008; 29(12): 1435–42. PubMed Abstract | Publisher Full Text | Free Full Text

14. Marini JC, Cabral WA, Barnes AM: Null mutations in LEPRE1 and CRTAP cause severe recessive osteogenesis imperfecta. Cell Tissue Res. 2010; 339(1): 59–70. PubMed Abstract | Publisher Full Text | Free Full Text
34. Valencia M, Caparrós-Martin JA, Sirerol-Piquer MS, Pepin MG, Schwarze U, Singh V, et al.: OASIS causes severe recessive osteogenesis imperfecta in humans. Hum Mol Genet. 2011; 20(8): 1595–609.

35. Christiansen HE, Schwarz U, Christiansen HE, et al.: Homozygosity for a missense mutation in SERPINF1, which encodes the collagen chaperone protein HSPP47, results in severe recessive osteogenesis imperfecta. Am J Hum Genet. 2010; 86(3): 461–73.

36. Alanyay A, Avagyan H, Camacone N, et al.: Mutations in the gene encoding the H2R protein FBXBP6 cause autosomal-recessive osteogenesis imperfecta. Hum Mol Genet. 2010; 19(18): 3849–63.

37. Keskukwim syndrome, a recessive congenital contracture disorder, extends the phenotype of osteogenesis imperfecta type V caused by a mutation in the FKBP10 gene. Am J Med Genet A. 2010; 153A(10): 2391–402.

38. Martínez-Glez V, Valencio M, Caparros-Martín JA, et al.: Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. Hum Mol Genet. 2012; 21(10): 2306–15.

39. Laine CM, Wessman M, Toivainen-Salo S, et al.: A novel splice mutation in PLOD3 causes X-linked early onset low-turnover osteoporosis. J Bone Miner Res. 2013; 28(3): 1010-8.

40. Cito TJ, Lee KE, Lee SK: A single recurrent mutation in the 5'-UTR of IFITM5 causes osteogenesis imperfecta type V. J Hum Genet. 2012; 57(2): 122–6.

41. Homan EP, Rauch F, Grafe I, et al.: Radiographic features of osteogenesis imperfecta type VI. J Bone Miner Res. 2012; 27(12): 2798–803.

42. Guillén-Navarro E, Ballesta-Martínez MJ, Valencia M, et al.: Two mutations in IFITM5 causing distinct forms of osteogenesis imperfecta. Am J Med Genet A. 2014; 164A(5): 1136–42.

43. Farber CR, Reich A, Barnes AM, et al.: A novel IFITM5 mutation in severe alkaptonuria osteogenesis imperfecta type VI impairs osteoblast production of pigment epithelium-derived factor. J Bone Miner Res. 2014; 29(6): 1402–11.

44. Keskukwim syndrome, a recessive congenital contracture disorder, extends the phenotype of osteogenesis imperfecta type V caused by a mutation in the FKBP10 gene. Am J Med Genet A. 2010; 153A(10): 2391–402.

45. Martínez-Glez V, Valencio M, Caparros-Martín JA, et al.: Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. Hum Mol Genet. 2012; 21(10): 2306–15.

46. Laine CM, Goeng KS, Campeau PM, et al.: WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. N Engl J Med. 2013; 368(19): 1809–16.

47. Simonsen S, Mallaf F, D’Hondt S, et al.: Deficiency for the ER-stress transducer OASIS causes severe recessive osteogenesis imperfecta in humans. Orphanet J Rare Dis. 2013; 8: 154.

48. Murakami T, Saito A, Hino S, et al.: Signaling mediated by the endoplasmic reticulum stress transducer OASIS is involved in bone formation. Nat cell biol. 2009; 11(10): 1205–11.

49. Cito TJ, Lee KE, Lee SK: A single recurrent mutation in the 5'-UTR of IFITM5 causes osteogenesis imperfecta type V. J Hum Genet. 2012; 57(2): 122–6.

50. van Dijk F, Zilkens MC, Michi D, et al.: PLS3 mutations in X-linked osteoporosis with fractures. N Engl J Med. 2013; 369(16): 1529–36.

51. Fahimi S, Majewski J, Al-Jallad H, et al.: Osteoporosis caused by mutations in PLS3: clinical and bone tissue characteristics. J Bone Miner Res. 2014; 29(8): 1805–14.

52. Choi DJ, Lee SI: The long bone deformity of OASIS in a patient with recessive osteogenesis imperfecta. Bone. 2013; 51: 164A.

53. Roschger P, Fratzl-Zelman N, Misof BM, et al.: Evidence that abnormal high bone mineralization in growing children with osteogenesis imperfecta is not associated with specific collagen mutations. Calcif Tissue Int. 2008; 82(4): 263–70.

54. Pazzaglia UE, Congiu T, Brandt C, et al.: The long bone deformity of OASIS in a patient with recessive osteogenesis imperfecta III: analysis of structural changes carried out with scanning electron microscopic morphometry. Calcif Tissue Int. 2013; 93(5): 453–61.
97. Nicolau N, Agraev V, Padman M, et al.: Changing pattern of femoral fractures in osteogenesis imperfecta with prolonged use of bisphosphonates. J Child Orthop. 2012; 6(1): 21–7. PubMed Abstract | Publisher Full Text | Free Full Text

98. Carpetano P, Del Frezzo JA, Ruiz-Sanz J, et al.: Alypical fracture in a child with osteogenesis imperfecta. J Orthop Surg. 2015; 32(4): 287–8. PubMed Abstract | Publisher Full Text

99. Malmgren B, Aström E, Söderhäll S: No osteonecrosis in jaws of young patients with osteogenesis imperfecta treated with bisphosphonates. J Oral Pathol Med. 2008; 37(4): 196–200. PubMed Abstract | Publisher Full Text

100. Cheshire CA, Cheung MS, Head TV, et al.: Tooth extraction socket healing in pediatric patients treated with intravenous pamidronate. J Pediatr. 2008; 153(5): 719–20. PubMed Abstract | Publisher Full Text

101. Henegue BA, Jayasinghe J, Khajeh J, et al.: Systematic review on the incidence of bisphosphonate related osteonecrosis of the jaw in children diagnosed with osteogenesis imperfecta. J Oral Maxillofac Res. 2014; 4(4): e1. PubMed Abstract | Free Full Text

102. Adamis S, Gati D, Colapietro F, et al.: Intravenous alendronate in adults with osteogenesis imperfecta. J Bone Miner Res. 2003; 18(1): 126–30. PubMed Abstract | Publisher Full Text

103. Chevrel G, Schott AM, Fontanges E, et al.: Bisphosphonate treatment in osteogenesis imperfecta: perspectives and controversies. Eur J Endocrinol. 2014; 170(5): 126–30. PubMed Abstract | Publisher Full Text

104. Shapiro JR, Thompson CB, Wu Y, et al.: Bone mineral density and fracture rate in response to intravenous and oral bisphosphonates in adult osteogenesis imperfecta. Calcif Tissue Int. 2010; 87(2): 120–9. PubMed Abstract | Publisher Full Text

105. Bradbury LA, Barlow S, Geoghegan F, et al.: Bisphosphonates in adults with osteogenesis imperfecta type I: increased bone mineral density and decreased bone turnover, but high fracture rate persists. Osteoporos Int. 2012; 23(1): 285–94. PubMed Abstract | Publisher Full Text

106. O’Sullivan ES, van der Kemp S, Kilbane M, et al.: Osteogenesis imperfecta in adults: phenotypic characteristics and response to treatment in an Irish cohort. Ir J Med Sci. 2014; 183(2): 225–30. PubMed Abstract | Publisher Full Text

107. Phillips CA, Remington T, Steiner RD: Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev. 2008; (4): CD003088. PubMed Abstract | Publisher Full Text | F1000 Recommendation

108. Halik JD, Evangelou E, Langdahl BL, et al.: Bisphosphonates for the prevention of fractures in osteogenesis imperfecta: meta-analysis of placebo-controlled trials. J Bone Miner Res. 2015; 30(6): 929–33. PubMed Abstract | Publisher Full Text | F1000 Recommendation

109. Antoniazzi F, Monti E, Venturi G, et al.: GH in combination with bisphosphonate treatment in osteogenesis imperfecta. Eur J Endocrinol. 2010; 163(3): 479–87. PubMed Abstract | Publisher Full Text | F1000 Recommendation

110. Noer R, Rama CA, Zanchetta JR, et al.: Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001; 344(19): 1434–41. PubMed Abstract | Publisher Full Text | F1000 Recommendation

111. Gatti D, Rossini M, Viapiana O, et al.: Teriparatide treatment in adult patients with osteogenesis imperfecta type I. Calcif Tissue Int. 2013; 93(5): 448–52. PubMed Abstract | Publisher Full Text | F1000 Recommendation

112. Cummings SR, San Martin J, McClung MR, et al.: Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; 361(8): 756–65. PubMed Abstract | Publisher Full Text | F1000 Recommendation

113. Hoyer-Kuhn H, Netzer C, Koerber F, et al.: Two years’ experience with denosumab for children with osteogenesis imperfecta type VI. Orphanet J Rare Dis. 2014; 9: 145. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

114. Hoyer-Kuhn H, Samer O, Stichova E: Effect of denosumab on the growing skeleton in osteogenesis imperfecta. J Clin Endocrinol Metab. 2014; 99(11): 3954–5. PubMed Abstract | Publisher Full Text

115. Boyce AM, Chong WH, Yao J, et al.: Denosumab treatment for fibrous dysplasia. J Bone Miner Res. 2012; 27(7): 1462–70. PubMed Abstract | Publisher Full Text | Free Full Text

116. McIlwain MR, Grauer A, Boonen S, et al.: Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. 2014; 370(5): 412–20. PubMed Abstract | Publisher Full Text | F1000 Recommendation

117. Sinder BP, Eddy MM, Ominsky MS, et al.: Sclerostin antibody improves skeletal parameters in a BrtlI/mouse model of osteogenesis imperfecta. J Bone Miner Res. 2013; 28(1): 73–80. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

118. Sinder BP, White LE, Salem JD, et al.: Adult BrtlI/mouse model of osteogenesis imperfecta demonstrates anabolic response to sclerostin antibody treatment with increased bone mass and strength. Osteoporos Int. 2014; 25(8): 2097–107. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

119. Roschger A, Roschger P, Keplinger P, et al.: Effect of sclerostin antibody treatment in a mouse model of severe osteogenesis imperfecta. Bone. 2014; 66: 182–8. PubMed Abstract | Publisher Full Text | F1000 Recommendation

120. Grafe I, Yang T, Alexander S, et al.: Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta. Nat Med. 2014; 20(6): 670–5. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

121. Horwitz EM, Prokop DJ, Gordon PL, et al.: Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood. 2001; 97(5): 1227–31. PubMed Abstract | Publisher Full Text

122. Horwitz EM, Gordon PL, Koo WK, et al.: Isolated allogeneic bone marrow-derived mesenchymal cells engraf and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone. Proc Natl Acad Sci U S A. 2002; 99(13): 8932–7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

123. Le Blanc K, Góthenström C, Ringsdén O, et al.: Fetal mesenchymal stem-cell engrafment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation. 2005; 79(11): 1607–14. PubMed Abstract | Publisher Full Text | F1000 Recommendation

124. Amin MT, Shazly SA: In utero stem cell transplantation for radical treatment of osteogenesis imperfecta: perspectives and controversies. Am J Perinatol. 2014; 31(10): 829–36. PubMed Abstract | Publisher Full Text | Free Full Text

125. Lindahl K, Kindmark A, Laxman N, et al.: Allele dependent silencing of collagen type I using small interfering RNAs targeting 3'UTR Indes - a novel therapeutic approach in osteogenesis imperfecta. Int J Med Sci. 2013; 10(10): 1333–43. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
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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.

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