Rare Metabolic Bone Diseases

Osteogenesis Imperfecta
Fibrous Dysplasia
Hypophosphatasia
Osteogenesis Imperfecta
Epidemiology

- Osteogenesis imperfecta (OI), also known as brittle bone disease, is a rare genetic disorder affecting approximately 1 in 10,000 individuals, although the rate has been estimated to be as low as 1 in 25,000. The prevalence of OI in the United States is not known, but it is estimated to affect 25,000 to 50,000 people.

- The most common types of OI are caused by mutations in the type I collagen genes \textit{COL1A1} or \textit{COL1A2} and are inherited in an autosomal dominant manner. Other, rarer, types of OI are caused by mutations in genes involved in cross-linking, hydroxylation, or mineralization of type I collagen and are inherited in an autosomal recessive manner. Some cases of OI are not inherited at all but are caused by \textit{de novo} mutations.

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Classical Genetic Inheritance Pattern

• When someone with an autosomal dominant form of OI has children, each child has a 50% chance of inheriting the mutated gene.

• The parents of individuals with autosomal recessive OI are typically unaffected, but each carry one mutated copy of the gene. When two carriers of an autosomal recessive form of OI have children, each child has a 25% chance to be affected, a 50% chance to be a carrier like each parent, and a 25% chance to be unaffected and not carry a copy of the mutated gene.

Clinical Presentation

- Osteogenesis imperfecta is characterized by bone fragility, often presenting as fractures with little-to-no trauma. In addition, some common clinical features of OI include short stature, long bone deformities, bone pain, low muscle mass, blue sclera, a triangular-shaped face, brittle teeth, hearing loss, and joint hypermobility.

- However, there are different types of OI with symptoms that range from mild to severe. In addition, the clinical manifestations of OI can vary widely in patients with the same form of disease. The next several slides cover some of the main types of OI and their typical clinical features.

### Classification of Osteogenesis Imperfecta Types

<table>
<thead>
<tr>
<th>OI Type</th>
<th>Inheritance</th>
<th>Affected Gene</th>
<th>Protein</th>
<th>Defect</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AD</td>
<td>COL1A1/COL1A2</td>
<td>α1(1) collagen</td>
<td>Collagen quantity</td>
<td>Mild, non-deforming</td>
</tr>
<tr>
<td>II</td>
<td>AD</td>
<td>COL1A1/COL1A2</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>COL1A1/COL1A2</td>
<td>α1(1)/α2(1) collagen</td>
<td>Collagen structure</td>
<td>Progressive deformity</td>
</tr>
<tr>
<td>IV</td>
<td>AD</td>
<td>COL1A1/COL1A2</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, and hyperplastic calcius</td>
</tr>
<tr>
<td>VI</td>
<td>AR</td>
<td>SERPINF1</td>
<td>PEDF</td>
<td></td>
<td>Moderate to severe</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>Severe to lethal</td>
</tr>
<tr>
<td>X</td>
<td>AR</td>
<td>SERPINH1</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>Progressive deformity, 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>AD</td>
<td>WNT1</td>
<td>WNT1</td>
<td></td>
<td>Variable severity, Early-onset osteoporosis</td>
</tr>
</tbody>
</table>

AD = Autosomal Dominant, AR = Autosomal Recessive

Type I

- This is the most common and mildest form of OI. Sometimes, it can be so mild that it isn’t diagnosed until adulthood.
- Affected genes: *COL1A1/COL1A2*
- Bone fractures occur mostly before puberty and decrease in frequency after puberty.
- Normal height; a few inches shorter than same gender relatives
- Little or no bone deformity
- Brittle teeth in rare cases
- Hearing loss in some cases
- Blue sclera (whites of the eyes)
- Easy bruising
- Mild delay in motor skills
Type II / III

• **Type II**
  - This is one of the most severe type of OI. It usually results in stillborn birth or death in the first months of life.
  - Affected genes: COL1A1/COL1A2
  - Severe bone deformity

• **Type III**
  - This is the most severe nonlethal form of OI
  - Affected genes: COL1A1/COL1A2
  - Hundreds of fractures starting very early in life
  - Severe bone deformities and physical disability that worsen over time
  - Sclera may be blue or grey
  - Triangular face and prominent forehead
  - Scoliosis
  - Sunken or protruding chest wall
  - Brittle teeth
  - Hearing loss
  - Very short height
  - Motor skill delays
  - Patients usually need wheelchairs

Eight year-old with typical facial features of type III OI.

Type IV

- Similar to type I but with mild to moderate bone deformity
- Affected genes: COL1A1/COL1A2
- Dozens of fractures on average, most of which occur before puberty or after middle age
- Motor skill delays
- Braces or crutches often needed to walk
- Short height
- Brittle teeth
- Hearing loss in some cases
- White or blue sclera
- Scoliosis
- Large head
- Easy bruising
Type V / VI

• **Type V**
  • Affected gene: *IFITM5*
  • Identical symptoms to Type IV except:
    • Normal sclera
    • Normal teeth
    • Severely limited ability to twist forearms clockwise or counterclockwise
  • Distinguished from Type IV by differing bone features at microscopic level
  • Hypertrophic calluses in large bones at fracture or surgical sites are a prominent feature. Hypertrophic calluses can also occur spontaneously.

• **Type VI**
  • Affected gene: *SERPINF1*
  • Identical symptoms to Type IV except:
    • Normal teeth
    • Greater frequency of fractures
  • Distinguished from Type IV by differing bone features at microscopic level
• Type VII and VIII
  • Affected gene: CRTAP (Type VII) and LEPRE1 (Type VIII)
  • Similar to Types II and III
  • Severe or lethal bone deformity
  • Type VII can also involve small head, blue sclera, bulging eyes
  • Some patients with Type VIII have lived into their second or third decade
Type IX / X

- **Type IX**
  - Affected gene: *PPIB*
  - Moderate to severe bone deformity and similar to Types III and IV
  - White sclera
  - Short height

- **Type X**
  - Affected gene: *SERPINH1*
  - Severe and often leads to death
Diagnosis

- Osteogenesis Imperfecta can often be diagnosed based solely on clinical features. Genetic tests, or a collagen biopsy test, can help confirm a diagnosis. Both the collagen biopsy test and genetic tests are thought to detect nearly 90 percent of all type 1 collagen mutations.

- Routine prenatal screening by ultrasound or genetic testing can achieve good results for patients with positive family histories. However the detection rate is very low where there is no family history.

Treatment: Pharmacologic Therapy

- Bisphosphonates are the primary treatment for children with moderate to severe OI. These drugs increase bone mineral density, and in observational studies they have been associated with lower fracture risk, decreased bone pain, improved vertebral shape, and increased ability to perform the activities of daily living.

- However, it has been difficult to confirm all of these benefits in randomized clinical trials, and the optimal duration of bisphosphonate treatment is not known.


The goals of physical therapy are to maximize mobility and decrease bone pain and fractures. Physical therapy 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. They may also require occupational therapy to help with daily living activities.

Treatment: Surgery

• Surgery is sometimes used to correct bone deformities, including scoliosis and basilar invagination. A common surgical procedure for OI patients, “rodding,” entails placing metal rods in the long bones of the legs. This strengthens the bones and helps prevent fractures. Surgical treatment is mainly performed to correct deformities, to reduce the bone brittleness that results from bad bowing, and to improve a patient’s physical condition.

Other Therapies for OI

• **Neridronate.** This aminobisphosphonate is not FDA approved, but it has been extensively studied in patients with OI. In growing children, neridronate treatment induces a rapid increase in bone mineral density and a significant decrease in fracture risk. Similar results have been obtained in newborns affected by the more severe forms of OI, with some evidence of improvement in the rate of skeletal growth. Neridronate has also been tested in adults, with evidence of efficacy for lowering fracture risk.

• **Estrogen.** Some researchers have proposed using estrogen to treat infant OI. One study in children found the combination of estrogen and neridronate was associated with superior results compared with bisphosphonates alone. However, few studies have evaluated this treatment.

• **Teriparatide.** Teriparatide is an anabolic agent that stimulates bone formation and resorption. This drug decreases vertebral and non-vertebral fractures in post-menopausal women with osteoporosis. A randomized trial of teriparatide in adults with OI showed increased bone mineral density and vertebral strength. Further research is needed to clarify the clinical benefits in adults. Teriparatide is not appropriate for children due to increased risk of bone cancer.

• **Stem Cell Transplantation.** This is a newly developed approach for managing OI. Transplanting mesenchymal stem cells has the potential improve the bone structure, growth, and fracture healing. Initial clinical results have been promising, and this therapy may be appropriate for some patients.

Fibrous Dysplasia
Fibrous dysplasia (FD) is a rare bone disease caused by postzygotic somatic mutations in the GNAS gene, resulting in normal bone being replaced with fibrous tissue. It may occur in a single bone (monostotic) or multiple bones (polyostotic). It is not an inherited disease. There are no verified cases of vertical transmission.

The lesions of FD typically manifest during the first few years of life, and they expand during childhood and adolescence. It is unusual for onset to occur after age 10. Clinically significant bone lesions are usually apparent by age 5. They are rare after age 15.

Fibrous dysplasia affects males and females equally. The exact incidence and prevalence of the disorder is not known. The monostotic form is three to four times more common than the polyostotic form.

A small subset of polyostotic cases (about 3%) occur along with endocrine abnormalities and café-au-lait spots, a triad called McCune-Albright syndrome.
Clinical Presentation

• The severity and specific symptoms of FD vary greatly from one patient to another. The disease is often asymptomatic and discovered incidentally when x-rays are performed for another reason. Conversely, some patients develop severe and potentially disabling or disfiguring symptoms.

• Fibrous dysplasia has a broad phenotypic spectrum, with disease potentially involving any part or combination of the skin, bone, and endocrine systems. Café-au-lait skin macules are typically the first manifestation and are apparent at or shortly after birth. These lesions characteristically reflect along the midline of the body and include jagged, irregular “coast of Maine” borders.
FD typically presents with fractures, deformity, limp, or pain. Repeated fractures and expansile deformities may lead to functional impairment and mobility problems. The proximal femorae may develop the classical “shepherd's crook” (coxa vara) deformity. Axial FD is common and in rare cases may result in severe and progressive scoliosis.

Note: This figure is from page 18 of the following source:
Endocrine Effects of FD

• Endocrine abnormalities associated with FD include:
  • Gonadotropin-independent precocious puberty resulting from recurrent ovarian cysts in girls and autonomous testosterone production in boys.
  • Testicular lesions with or without associated gonadotropin-independent precocious puberty.
  • Thyroid lesions with or without non-autoimmune hyperthyroidism.
  • Growth hormone excess.
  • FGF23-mediated phosphate wasting with or without hypophosphatemia in association with fibrous dysplasia.
  • Neonatal hypercortisolism.

Diagnosis

• The diagnosis of FD is based on a combination of clinical, radiographic, pathologic, and molecular information. In patients whose only clinical feature is monostotic FD, biopsy and identification of a somatic GNAS mutation may be required for diagnosis.

• However, experienced clinicians or radiologists will often note that a lesion appears “characteristic of FD” on radiographic exam, establishing an FD diagnosis without the need for biopsy.

• Computerized tomography and magnetic resonance imaging may be used to evaluate bone and assess the extent of disease. The lesions of FD resemble ground glass when seen on x-ray. Radionuclide bone scintigraphy is also useful for determining the extent of disease.

• Clinical management of FD is best accomplished by a multidisciplinary team of specialists. Treatment should focus on optimizing function, minimizing morbidity related to fractures and deformity, and addressing any endocrine effects of the disease.

• No medical therapies have proven effective for treating FD. Antiresorptive therapy with bisphosphonates has been advocated due to the high levels of bone resorption seen in FD tissue. Bisphosphonates are not likely to alter the course of the disease, but more potent intravenous formulations may be effective for treating FD-related bone pain.

• Patients with FD are at risk for osteonecrosis of the jaw as a consequence of bisphosphonate therapy. To minimize this risk, intravenous bisphosphonates should be used at the lowest possible dose and interval.

• There is little data to inform surgical indications or techniques. Curettage, grafting, plates and screws, and other external fixation devices are frequently ineffective and should generally be avoided. Intramedullary devices are preferred for treating fractures and deformity in the lower extremities, and scoliosis can be managed with standard instrumentation and fusion techniques.

Hypophosphatasia
A Rare Genetic Disorder

• Hypophosphatasia (HPP) is a rare inherited disorder characterized by the abnormal development of bones and teeth. The disease is caused by loss-of-function mutations in the tissue nonspecific alkaline phosphatase (TNSALP) gene, also called the ALPL gene. This is the only gene known to be involved in HPP. Defects in TNSALP impair the mineralization process, which results in tooth loss and weak bones that are prone to fracture and deformity.

• Scientists have identified more than 300 predominantly missense mutations of TNSALP associated with HPP, which explain the many types of this disease and the wide variety of symptoms and their severity.
The prevalence of the most severe form of HPP is estimated to be between 1 in 100,000 and 1 in 300,000. The prevalence of milder forms is higher, and has been estimated to be as high as 1 in 6,370 individuals. In the United States, approximately 500-600 individuals with HPP have been identified.

However, the overall incidence and prevalence of all forms of HPP is not truly known. Milder cases are often undiagnosed or misdiagnosed, making it difficult to determine the true frequency of HPP in the general population.

Clinical Presentation

• The signs and symptoms of HPP vary widely and appear anywhere from before birth to adulthood. The most severe forms typically occur before birth and in early infancy. Severity of the disease ranges from death in the perinatal period to dental problems or fractures in adulthood.

• HPP has been classified into five categories based on age of onset. These are discussed in the following slides.
The clinical features of perinatal HPP are typically discovered at birth or before based on a prenatal ultrasound. These include obvious skeletal abnormalities, including chest wall deformities, as well as short or bowed long bones. The skeleton is hypomineralized, which is readily identified on X-ray. Perinatal HPP is almost universally fatal shortly after birth.

Bacon S and Crowley R. “Developments in rare bone diseases and mineral disorders” Therapeutic Advances in Chronic Disease 2018; 9:51-60.
Infantile HPP

- Infantile HPP is usually diagnosed by six months of age. Fractures are common, and the characteristics of rickets are seen on X-ray. Infants with HPP present with failure to thrive and respiratory distress. Craniosynostosis and seizures are common. Biochemical abnormalities include a low serum alkaline phosphatase (hypophosphataemia), hypercalcaemia, hypercalciuria, and resultant nephrocalcinosis. Mortality from infantile HPP is substantial.

Bacon S and Crowley R. “Developments in rare bone diseases and mineral disorders” Therapeutic Advances in Chronic Disease 2018; 9:51-60.
Childhood HPP manifests after six months of age. Clinical features include myopathy, delays in gross motor development, low bone mass, poorly healing fractures, and premature loss of deciduous teeth with the root intact. Imaging reveals changes of rickets and often a radiolucent band extending from the growth plate into the metaphysis.

Bacon S and Crowley R. “Developments in rare bone diseases and mineral disorders” Therapeutic Advances in Chronic Disease 2018; 9:51-60.
Clinical characteristics of adult HPP are often subtle and include osteoporosis, recurrent fractures, and crystal arthropathy. Patients commonly present with nonspecific musculoskeletal complaints. Many adults with HPP had symptoms during childhood, but the diagnosis was missed.
Odontohypophosphatasia

- This is the least severe form of HPP. It manifests in children and adults and is characterized by premature loss of primary or permanent teeth and severe dental caries.

Bacon S and Crowley R. “Developments in rare bone diseases and mineral disorders” Therapeutic Advances in Chronic Disease 2018; 9:51-60.
Images of HPP

Figure 2 Skeletal and dental defects associated with hypophosphatasia.

Diagnosis

- HPP can usually be diagnosed with a medical history, physical examination, laboratory findings, and imaging. Genetic tests for TNSALP gene mutations are not required but can be used if necessary.

- Adult patients are often asymptomatic, and the diagnosis is made by chance. Adults with HPP may come to clinical attention by finding low serum alkaline phosphatase (ALP) on routine laboratory testing or during an evaluation for osteoporosis or fractures.

- If repeat testing confirms low serum ALP, and other causes of low ALP are eliminated, elevated serum pyridoxal 5’-phosphate (vitamin B6) and/or elevated urinary phosphoethanolamine (PEA) support the diagnosis of HPP. In some patients, only one of these biomarkers may be elevated.

- In children, the disease can be identified by its clinical features and imaging. Severely hypomineralized bone is a hallmark of perinatal and infantile HPP. Childhood HPP will exhibit metaphyseal changes of rickets and bands of radiolucency extending from the growth plate into the metaphysis.


Treatment in Children: Enzyme Replacement Therapy

• In 2015, the U.S. Food and Drug Administration approved Stremsiq (asfotase alfa), an enzyme replacement therapy employing bone-targeted recombinant human TNSALP, to treat perinatal, infantile, and juvenile-onset HPP. This is the only approved medication for HPP.

• In patients with perinatal and infantile HPP, enzyme replacement therapy has been shown to heal the skeletal manifestations of the disease; improve skeletal mineralization, respiration, and motor function; resolve scoliosis and reduce deformity; and significantly improve survival.

• In children with HPP, enzyme replacement therapy has been shown to increase height, weight, muscle strength, and motor skills. In adolescents and adults, it has reduced bone pain and fractures and improved physical functioning and quality of life.


Treatment in Adults

• There is no approved or established treatment of HPP in adult patients. The recombinant parathyroid hormone teriparatide has shown an improvement of fracture healing and stress fractures in some patients. The use of the newer anabolic agent abaloparatide has not been studied.

• Management of adult HPP requires a multidisciplinary approach to prevent and treat bone and joint complications, to mitigate chronic pain, and to improve quality of life.

Other Treatment Considerations

• For children and adults, treatments should be tailored to the specific symptoms and complications of each patient. For some patients, treatment may require the coordinated efforts of a team of specialists including pediatricians, orthopedic surgeons, dentists, pain management specialist, and others.

• Non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat bone and joint pain. Vitamin B6 can help control specific seizures in severely affected infants. Infants that develop hypercalcemia may be treated with dietary calcium restriction, hydration, diuretics, and calcitonin.

• Regular dental care beginning at year 1 is recommended. Physical and occupational therapy may also be necessary.

Rush ET. “Childhood hypophosphatemia: to treat or not to treat” Orphanet Journal of Rare Diseases 2018; DOI: /10.1186/s13023-018-0866-7
Surgery

- Adults with repeated long bone fractures may be treated by an orthopedic internal fixation ("rodding").
- If craniosynostosis causes intracranial pressure, surgery may be necessary to relieve that pressure.

Avoid Bisphosphonates!

- Clinicians should take care to avoid certain medications commonly used for osteoporosis that might be harmful in patients with HPP. Bisphosphonates and denosumab may exacerbate the symptoms HPP. Any potent antiresorptive agent could lower serum ALP, which is already low in these patients.
- In addition, excessive vitamin D intake may aggravate hypercalcemia and hypercalciuria.

Bacon S and Crowley R. “Developments in rare bone diseases and mineral disorders” Therapeutic Advances in Chronic Disease 2018; 9:51-60.