Osteogenesis Imperfecta

Abstract

Osteogenesis imperfecta (OI) is a genetic disorder of connective tissue characterized by brittle bones. Other characteristics are poorly formed teeth, blue sclera of the eye, and hearing loss. Four classifications of OI were categorized in 1979 and 3 other classifications have been made since then and are still used today. Bisphosphonate therapy and surgical interventions are treatment options for OI patients.

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder of connective tissue characterized by bones that break easily, often from little or no apparent cause. It is also known as “brittle bone disease.” OI affects both males and females equally throughout the world. Prevalence of the disorder is estimated to be 1 in 10,000 births. OI is caused by mutations of the type-1 collagen gene. Collagen is a protein that strengthens and supports many tissues in the body including cartilage, bone, tendon, skin, and the sclera of the eye. “OI mutations result in the production of too little type-1 collagen or of poor-quality collagen.” The mutations that occur are of varying degree depending on the severity of the disorder. Mild forms include no deformity, near normal stature, and few fractures. Severe forms include skeletal malformations such as bowed extremities, scoliosis, and some forms are lethal in the perinatal period.

Types of Osteogenesis Imperfecta

Four classification of OI were identified by Sillence et al in 1979, and “are based on age of onset, clinical and radiographic features and disease severity. Although some overlap occurs in between types, the 4 main classifications provide relatively straightforward and useful distinctions in most cases.”
**Type I**

Type I OI is also known as mild OI. Type 1 is the result of lower than normal amounts of collagen while the 3 other types of OI result from the defect in the structure of collagen.\(^1\) Type I patients have a smaller body stature and triangular face with mildly prominent frontal bones and narrowing jaw. The sclera, or white part of the eyes, differ in color from pale blue to deep blue. Bone fragility and scoliosis are common in these patients. Type I patients typically experience 5 to 15 fractures before puberty. After onset puberty, the fracture rate in Type I patients drops significantly.\(^1\) According to Sillence, 40% of his patients with Type I OI had severe hearing impairment requiring a hearing aid, with 35% of his overall patients having proven or suspected hearing loss.\(^7\) 45% to 50% of OI cases are in the Type I category.\(^1\)

**Type II**

Type II OI is also known as lethal OI. It is the most severe form due to the inadequate bone growth while the fetus is in the womb. The condition is usually fatal to newborns. Death normally results from respiratory failure associated with the distortion of the ribcage or thoracic cavity.\(^2\) Death can also occur from “brainstem compression or intracranial hemorrhaging.”\(^1\) Bone fragility is very evident after birth of the infant. Sillence et al\(^7\), upon looking at skeletal x-rays of the infants, described the appearance of the bones as “crumpled (concertina-like or accordion-like) femora, marked angulation of tibiae and sometimes femora, fractures and deformity of the shafts of the upper limbs, platyspondyly, and a beaded appearance of the ribs”\(^7\)(p.106) Type II OI occurs in 10% of cases of OI.\(^1\)

**Type III**

Type III OI is the most severe form of OI that is survivable.\(^2\) Type III OI is evident upon birth like Type II. Birth weight and length are lower than average. Severe physical disability is associated with Type III OI. Fractures are present at birth and bones continue to fracture easily. Deformities and frequent fractures often confine these patients to a wheelchair for life.\(^2\) Distortion of the spine and rib cage can cause pulmonary and respiratory problems that can worsen with age.\(^1\) The triangular face present in Type I OI is also associated with Type III OI. Scoliosis and kyphosis are commonly seen in these patients. Long bone deformity or bowed
bones are frequently seen in Type III OI. Blue sclera is also present. Type III is seen in 20% of cases of OI.  

**Type IV**

Type IV is also known as moderately severe OI. This type of OI is a combination of Type I and III and can range from mild to moderately severe. Type IV patients may be born with blue sclera but as they grow the coloration lessens to almost white. Fractures of the bones may or may not be preset at birth. Skeletal deformity in the spine, thorax, and long bones is less severe than Type III but more than Type I. Bowing and fracturing of the long bones can still occur that can “lead to deformity and difficulty in walking and moving. Some patients with Type IV OI deal with difficulties by using canes, crutches, or wheelchairs.” Dentinogenesis imperfecta (DI), the discoloration and abnormal development of teeth, is also frequent. Type IV OI occurs in 20% of patients.

**Additional Types of Osteogenesis Imperfecta**

Additional types of OI have been identified since Sillence et al’s study of OI in 1979. These types have been identified though investigations that involved patients with OI, thought to have Type IV, but with distinct patterns on their bones not shared by patients who have Type IV OI.

**Type V**

Type V OI is very similar to that of Type IV in bone fragility. The sclera and teeth of these patients appear unaffected by OI. The difference in Type V OI is the appearance of the biopsied bone. “Bone biopsies reveal decreased cortical and cancellous bone and irregularly orients trabeculae. This bone has a “mesh-like” appearance when viewed under a microscope.” These patients are present with large calluses, called hyperplastic calluses, that develop around injury sites or surgical sites. “These patients present with hard, painful, and warm swellings over bones that initially may suggest inflammation or even an osteosarcoma.” There is also evidence of calcifications of the interosseous membrane in between long bones, such as in between the tibia and fibula, and the radius and ulna. This type of
OI does not show evidence of the mutation of type-1 collagen. The genetic mutation responsible for this type is yet to be identified. Type V OI is associated with 5% of OI cases.¹

**Type VI**

Type VI is very similar to the moderately severe forms of OI. Patients with type VI have light blue to white sclera. There are no signs of DI either. Evidence also shows vertebral compression fractures on all patients with this type of OI.¹ Blood tests show an elevated level of alkaline phosphate, which is an enzyme linked to bone formation.² “The bones of patients with Type VI OI have a “fish scale” appearance under a microscope. The genetic mutation responsible for Type VI OI remains unknown.”¹⁰(p.539)

**Type VII**

Type VII ranges from moderate to severe OI. Patients can show fractures at birth, blue sclera, shortened limbs, and specifically coxa vera, which is a shortening of the femoral neck. Type VII OI results from the “mutations of the cartilage-associated protein (CRTAP) gene rather than from collagen-related mutations.”¹⁰(p.539) Bone biopsies reveal that it looks closely like Type I OI.¹

**Associated Disorders**

Brittle bones are not the only trait of OI. OI can also affect the patient’s teeth, hearing, and sclera of the eye. This is because of the lack of collagen and the mutation of the type-1 collagen. Some of the disorders that affect OI patients are dentinogenesis imperfecta, hearing loss, and blue sclera.

**Dentinogenesis Imperfecta**

Dentinogenesis imperfecta (DI) is a defect of the dentin in the teeth.¹²,⁸ It is a common trait in Types I, III and IV OI.¹ DI presents the patients with misshapen and discolored teeth. Colors can appear as purple, brown or opalescent. In Abukabos and Al-sineedi’s case report⁸, they reported “About 50% of children and adults with OI have dental involvement of varying degree and severity… Teeth with DI have certain features, including amber bulbous crowns or
gray-brown discoloration... narrow roots, partial or total obliteration of pulp chambers, and root canals with evidence of periapical radiolucencies."⁷(p.160) Enamel, the outside layer of the tooth, is visibly chipped and discolored and may have excessive tooth decay (see Figure 1).¹ Treatments for DI include placement of artificial crowns on the teeth as soon as they come in. Other treatments include observation of the development of the facial bones, active follow-up, bleaching of the teeth and good oral hygiene.⁸

**Hearing Loss**

Hearing loss appears most common in Type I OI. Symptoms usually appear between the ages of 20 and 30.¹⁵ Kuririla et al⁵ conducted a study of 133 patients, between the ages of 17 and 81 years, all of which were diagnosed with OI. In their study, “hearing loss was found to be progressive and bilateral, beginning predominantly in the second to fourth decades of life.”⁷(p.944) They also found that 60.4% of Type I OI patients and 42.3% of Type IV OI patients in their study had hearing loss. There was also no correlation between the frequency or severity of the hearing loss between the types of OI. It was concluded that “hearing loss is a common feature in OI, affecting patients with all types of OI.”⁷(p.945)

**Blue Sclera**

Sclera, the white part of the eye, is usually tinted blue among OI patients. This, like other problems that come with OI, is because of lack of collagen in the eye. The layers of the eye tissue are very thin in OI patients, “which allows the choroid layers beneath the sclera to be seen.”¹(p.541) The color of the sclera ranges from very light blue to darker shades of deep blue. As the patients ages, the intensity of the blue decreases.¹

**Treatment of Osteogenesis Imperfecta**

Treatment of OI varies from patient to patient depending on the severity of the OI. “The primary objective of OI therapy revolves around decreasing the number of pathologic fractures, decreasing pain, increasing growth, improving bone metabolism, and optimizing function.”⁶(p.567) Both pharmaceutical and surgical interventions can be made.
**Pharmaceutical Intervention**

The main pharmaceutical treatment for OI is the use of bisphosphonates (BP). “Since the 1990s, bisphosphonates have been used successfully in OI. In well-controlled studies, it has been shown that by using [BP] in children with OI, mineralized bone tissue and bone strength will increase.”4(p.431) BP therapy prevents the loss of bone mass by inhibiting the digestion of bone that occurs in normal everyday bone growth. BP’s encourage osteoclasts, which destroy bone faster with those who have OI, to die; thereby slowing bone loss. Treatments with BP can be done intravenously or orally. One type of oral bisphosphonate is risedronate. It prevents bone breakdown and increases bone mineral density (BMD) “in children with mild to severe osteogenesis imperfecta, and reduced long-bone bowing deformities.”3(p.1425)

An international study done by Bishop et al3, including patients in 20 different hospitals in 13 different countries across North and South America, Europe, Africa and Australia, investigated the safety and efficacy of risedronate in children with OI. One-hundred and forty-seven patients, ages 4 to 15 were randomly assigned a treatment of risedronate (94 patients) or a placebo (49 patients). A dosage of 2.5 or 5 mg of risedronate was given according to age, weight and height. Data showed that at the end of the first year, lumbar spine BMD had a mean increase of 16.9% in the risedronate group and 7.6% increase in the placebo group. Clinical fractures also occurred in 31% of the risedronate group and 49% of the placebo group in the first year. After the first year, all patients were given open-label risedronate. In the next 2-3 year phase, clinical fractures were reported in 53% of the patients who received the risedronate since the beginning of the study and in 65% of the patients that began the study with the placebo.

The study of Bishop et al3 found that using the oral risedronate increased the areal BMD and reduced the risk of first and recurrent clinical fractures in children with OI. Results showed risedronate reduced the risk of recurrent clinical fractures by 42% after the first 12 months. The drug also showed that it was well tolerated among the patients in regards to gastrointestinal or musculoskeletal events. It was also reported that there was an increase in mobility and physical activity of the children receiving bisphosphonate treatment.

BP treatment can also be done intravenously. Zeitlin et al9 did a study on the weight and height of patients who had intravenous treatment with the BP compound pamidronate. They tested patients with Types I, III, and IV OI, who had undergone surgical rodding of the femur and/or tibia. Data was taken before the surgery, and every year for 4 years after the surgery had
taken place. The medication was administered intravenously in cycles of 3 consecutive days every 2, 3 or 4 months depending on the age of the patient. Each patient’s final yearly dose was 9 mg/kg. After 1 year of treatment, height scores increased significantly for Type III but had not statistically changed for Types I and IV. Baseline weight had not changed for Type III and for IV but increased for Type 1 OI. After 4 years of pamidronate therapy, mean height and weight scores had increased for all OI types tested. They also did a separate study on 15 patients who did not receive surgical rodding of the lower extremities, but were given pamidronate therapy for at least 3 years. It was found that there was a 7% ± 6.2% height increase on those patients who received treatments without having rod surgery.

The study of Zeitlin et al found that patients who received pamidronate therapy have an increase in height when compared to similar OI patients who do not receive therapy. There was an 11% height increase in Type III OI, 12% increase in Type IV OI, and 5% increase in Type I OI. “Long term pamidronate therapy is associated with significant height gain as compared with untreated OI patients with the same type of disease. Some children with OI gain weight excessively during pamidronate treatment.”

**Surgical Management**

Surgical rodding is a common management for OI to “control repeated fractures and improve bone deformities that interfere with function…Rodding is a surgical intervention that internally splints long bones with insertion of a metal rod into the bone’s internal cavity, the medullary cavity.” Not all OI patients need rodding surgery. Rodding is mostly done on patients who have frequent fractures or bone deformities. Intramedullary rods are preferred over internal fixation with plates and screws because the bone above or below the plate can become more prone to breakage. The bones most likely to need rodding are the femur and tibia.

The rods that are preferred are telescoping rods. These rods can move and elongate as the patients grows. The rod most currently used today is the Sheffield telescoping rod system with a T-piece fixation (see Figure 2). The rod is inserted at the proximal end of the bone and the T-piece of the rod is fixated in the proximal epiphyses of the bone. Another T-piece is at the distal end and fixated in the distal epiphyses. This allows for the bone to grow and still have the rod telescope out as the bone elongates.
Cho et al\textsuperscript{10} developed a modification of the telescopic rod system in which the distal end had a simple rod with a hole, instead of a T-piece. In the hole they put an interlocking pin in the distal epiphyses (see Figure 3).\textsuperscript{10} It was noted that “insertion of the distal [T-piece] is more invasive than is insertion of the proximal sleeve in both femur and the tibia, as it requires an arthrotomy of the distal joint, which may damage the articular cartilage. Installation [of a] T-piece into the [distal] tibia is even more traumatic requiring complete dislocation of the ankle joint or medial malleolar osteotomy.”\textsuperscript{10}(p.1028-1029) Cho et al’s\textsuperscript{10} modification does not require an arthrotomy for insertion of the pin in the distal epiphyses (see Figure 4). This prevents damage to the ligaments and articular cartilage of the ankle or knee.

Another surgical procedure that can be done in OI patients is spinal fusion. “The reported prevalence of scoliosis in patients with osteogenesis imperfecta is high, ranging between 39% and 88%. Factors contributing to the development of scoliosis include ligamentous laxity, muscle weakness, and vertebral fracture and deformity.”\textsuperscript{11}(p.238) This results in “growth disturbances of the chest and trunk that lead to exotic deformity of the spine. Scoliosis in OI is rigid and commonly progresses until thoracic insufficiency syndrome is present. In these cases, the chest collapses as the spinal deformity worsens.”\textsuperscript{12}(p.94) As this happens, the chest cavity becomes undersized and is not sufficient for the lungs to have proper expansion and development. Ribs can also be deformed and displaced (see Figure 5).\textsuperscript{12} Spinal fusion helps to prevent the spine from further curvature and elongates the chest cavity for better breathing. This procedure involves fusing vertebrae together with bone grafts or metal rods (see Figure 6).\textsuperscript{1}

Both rodding of the extremities and spinal fusion are found to have a better outcome and healing with the use of BP therapy before and after surgery. This helps the bones be able to heal faster and to have more strength along the diaphysis.\textsuperscript{10} Since the introduction of BP therapy, “patients can now have rodding surgery as early as 18 months of age without complications”\textsuperscript{2}(p.528)

Conclusion

OI is a complex disease that ranges in a variety of clinical presentations. The wide spectrum has led to the discovery of the different types of OI, the genetics of OI patients and the causes behind it. The physical disorders associated with OI patients are brittle bones, DI, hearing loss and blue sclera of the eyes. Studies have shown ways to improve bone density and strength
by using oral or venous bisphosphonate therapy. More advanced surgical procedures are also used today to help elongate the bones and to function properly. With the use of both BP therapy and surgical intervention, patients with OI can have a better outcome and can live normal lives.
References


Figures and Captions

Figure 1. (a-c) Images of 4-year old boy with Dentinogenesis Imperfecta. The patient was diagnosed with Type IV OI. Note the discoloration on all 3 views with yellow brown opalescent color and rapid wear. Image courtesy of: Abukabbos H, Al-Sineedi F. Clinical manifestations and dental management of dentinogenesis imperfecta associated with osteogenesis imperfecta: case report. Saudi Dent J. 2013;25(4):159-165.
Figure 3. Schematic drawing of the surgical procedure for insertion of an interlocking telescopic rod in the tibia (Fig. 2-A) and the femur (Fig. 2-B). Note the pin in the epiphyses of the distal bone. Image courtesy of: Cho TJ, Kim JB, Lee JW, et al. Fracture in long bones stabilized by telescopic intramedullary rods in patients with osteogenesis imperfecta. Journal of Bone & Joint Surgery, British Volume. 2011;93(5):634-638.
Figure 4. Anteroposterior and lateral radiographs of the right tibia of a five-year-old boy with Type IV OI. Marked angulation of the tibia (A) was corrected with use of an interlocking telescopic rod (B), which telescoped successfully for three years (C). Image courtesy of: Cho TJ, Kim JB, Lee JW, et al. Fracture in long bones stabilized by telescopic intramedullary rods in patients with osteogenesis imperfecta. Journal of Bone & Joint Surgery, British Volume. 2011;93(5):634-638.
Figure 5. (A) Anterior-posterior radiograph of 7-year-old female patient prior to surgery. Note appearance of scoliosis and abnormal chest cavity, leading to thoracic insufficiency syndrome. (B) On lateral radiograph of the spine, severe kyphosis is also noted. Image courtesy of: Kaplan L, Barzilay Y, Hashroni A, Itshayek E, Schroeder JE. Thoracic elongation in type III osteogenesis imperfecta patients with thoracic insufficiency syndrome. Spine. 2013;38(2):E94-e100.