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Research Article

Understanding Osteogenesis Imperfecta: Causes, Diagnosis and Treatment

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ABSTRACT

Osteogenesis imperfecta is a group of genetic disorders characterized by brittle bones and increased risk for fracture. Its management requires an interdisciplinary approach. Here we describe the basis of osteogenesis imperfecta, as well as diagnosis, treatment and future direction.

Keywords: Osteogenesis; Dentinogenesis imperfecta

INTRODUCTION

Osteogenesis Imperfecta (OI) is a group of rare genetic connective tissue disorders primarily characterized by bone fragility and skeletal deformities. It is caused by mutations in type I collagen (Col I) genes or related pathways involved in collagen synthesis, processing, and osteoblast differentiation [1]. The disease presents with a broad spectrum of severity, classified into five major types based on clinical and radiographic features.

Osteogenesis imperfecta, also known as brittle bone disease, refers to genetic connective tissue disorders characterized by bone fragility and increased risk of fracture [2–11]. It is estimated that osteogenesis imperfecta occurs in 1 per 15,000 to 20,000 live births in Western countries, with the prevalence being higher in certain populations [1,12–15]. The disorder exhibits wide phenotypic variability and corresponding clinical manifestations observed in the disorder, which can complicate diagnosis, treatment, and prognosis. Here we review osteogenesis imperfecta, including features, subtypes, diagnosis, both conventional and emerging treatment options, and overall management.

Genetic basis and subtypes of osteogenesis imperfecta

Mutations in genes involved in collagen structure or collagen synthesis are the primary cause of osteogenesis imperfecta [9,16–19]. The disorder is most commonly inherited in an autosomal dominant way, but recessive inheritance and de novo mutations also occur. Most cases of osteogenesis imperfecta result from mutations in the COL1A1 and COL1A2 genes, which affect collagen synthesis and structure and contribute to bone fragility [9].

Glycine substitutions and biallelic variants in these genes are associated with more severe phenotypes than what is observed with haploinsufficiency of collagen type Iα chains [20]. These mutations cause defects in collagen formation, which compromises the integrity and strength of bone. Additionally, more than 20 other mutations with implications for collagen integrity have also been identified as being associated with osteogenesis imperfecta [11].

Up to 90% of osteogenesis imperfecta cases are autosomal dominant inheritance of COL1A1 or COL1A2 [21]. X-linked inheritance and de novo mutations are associated with rare forms of osteogenesis imperfecta [22]. Some mutations, rather than affecting collagen, affect osteoblast differentiation or mineralization of bone [23].

There are 7 subtypes of osteogenesis imperfecta [24–28]. Notably, Type I is associated with mild symptoms, whereas Type II is lethal in newborns, and Type III is progressive. Even within the same subtype, there is a large degree of phenotypic variability. Details of the 7 types include:

Type I: Type I is mild and non-deforming and associated with blue sclera. If growth abnormalities occur, they are minor, and dentinogenesis imperfecta does not occur. A premature stop

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codon in the COL1A1 gene is the mutation most commonly associated with Type I [29].

Type II: Type II is perinatal lethal and associated with dark sclera. Multiple fractures in the ribs and long bones are present at birth, along with significant deformities and skull bones that are of abnormally low density. Glycine substitutions in the COL1A1 gene or COL1A2 gene are usually present in Type II osteogenesis imperfecta.

Type III: Type III is severely deforming and associated with greyish sclera. Dentinogenesis imperfecta is present, along with severe scoliosis, a triangular face, and significant growth deficits. Glycine substitutions in the COL1A1 gene or COL1A2 gene are usually present in Type III osteogenesis imperfecta.

Type IV: Type IV is moderately deforming and associated with white or greyish sclera. Dentinogenesis imperfecta is present, along with scoliosis and moderately short stature. Glycine substitutions in the COL1A1 gene or COL1A2 gene are usually present in Type IV osteogenesis imperfecta.

Type V: Type V is moderately deforming and associated with white sclera. There is no dentinogenesis imperfecta. Short stature is mild to moderate, and there is dislocation of the radial head, hyperplastic callus, and mineralized interosseous membrane. The genetic basis of Type V is unknown.

Type VI: Type VI is moderately to severely deforming and associated with white sclera. There is no dentinogenesis imperfecta. Short stature is moderate, and there is scoliosis present, along with an accumulation of osteoid within bone tissue and bone lamellation that is in a fish-scale pattern. The genetic basis of Type VI is unknown.

Type VII: Type VII is moderately deforming and associated with white sclera. There is no dentinogenesis imperfecta. There is mild short stature that involves short femora and humeri. The genetic basis of Type VII is unknown.

Mild forms of osteogenesis imperfecta are often not diagnosed until later in childhood or early adulthood when the individual endures a fracture or begins suffering hearing loss [11]. The more moderate severity forms of osteogenesis imperfecta tend to be diagnosed between the ages of 1 and 5 after the child has suffered multiple fractures or growth abnormalities are recognized [30]. Severe osteogenesis imperfecta may be diagnosed in utero or at birth when prenatal ultrasound or radiographs reveal relevant signs, such as multiple fractures or skeletal deformities [31].

Clinical evaluations and radiographic imaging may be used to support diagnosis [32–36]. In addition to x-rays and ultrasound, Dual-Energy X-Ray Absorptiometry (DXA) are often employed, as it can detect abnormalities in bone mineral density and bone mass. However, genetic testing is generally needed for a definitive diagnosis of osteogenesis imperfecta, particularly in milder cases where clinical and radiographic data may not provide clear evidence of osteogenesis imperfecta [11].

Osteogenesis imperfecta is associated with several predictable clinical manifestations

Osteogenesis imperfecta affects the skeleton, joints, soft tissues, muscles, and senses. Cardiorespiratory complications due to chest wall deformities and delayed healing are also common [1].

Bone abnormalities often lead to short stature in osteogenesis imperfecta, as well as in spinal and lower leg deformities (Figures 1-3). Scoliosis and bowed legs are particularly common in osteogenesis imperfecta, leading to pain, joint stress, and complications. These skeletal abnormalities may be progressive in severe forms of the disorder [29,31]. Fractures, caused by improper mineralization, are most frequent in childhood and adolescents with rates decreasing in adulthood [37]. Teeth are also prone to fractures, weakness and discoloration due to dentinogenesis imperfecta [1,38].

Joint and soft tissue abnormalities result in osteogenesis imperfecta from the lack of integrity of the bone and connective tissue, and include joint hypermobility and ligament laxity [1]. Muscle hypotonia also occurs, likely due to impaired osteoblast differentiation leading to reductions in muscle mass and strength [1].

Sensory impairments occur secondary to defects in collagen that impact multiple organ systems. Thinning of connective tissue in the eyes can lead to ocular deficits, and blue sclera are frequently observed in mild forms like Type I [39]. Also common in Type I is hearing loss, which occurs in 50-60% of adults with osteogenesis imperfecta [1,40]. Hearing loss is often progressive and may have several causes including deformities in the ossicles, excessive bone growth in the middle ear, defective collagen in the cochlea [40].

Multidisciplinary treatment and monitoring are necessary for optimizing outcomes

A multidisciplinary approach is necessary to optimize outcomes. A range of specialists are often needed throughout the lifetime of patients with osteogenesis imperfecta [30]. Goals of treatment for osteogenesis imperfecta include reducing the risk of fractures, improving bone strength, and reducing symptom burden [31–33,41–47]. Pharmacological treatments include biphosphates such as pamidronate, risedronate, and zoledronic acid, which can improve bone density and reduce bone resorption [31,48–52]. These medications have been shown to decrease pain, reduce fracture frequency, and improve mobility [30]. Early intervention with bisphosphates is associated with improved outcomes in osteogenesis imperfecta [53]. Other pharmacological interventions targeting relevant pathways include TGF-β inhibitors to improve bone strength, teriparatide to promote bone formation, and denosumab to reduce bone resorption [2,48,54].

Physical therapy and surgical interventions are common [31,48–52]. Physical rehabilitation can improve performance of daily activities and enhance participation in social activities through its positive impact on physical capabilities [11]. With better balance and stronger muscles, fracture frequency may also be reduced indirectly by a minimization of the risk of falls [30]. Mobility challenges necessitate assistive devices such as wheelchairs for some patients, and rehabilitation programs can support the use of these devices [11,30]. Surgical procedures, such as osteotomies and intramedullary rodding, stabilize bones and improve quality of life [55,56] (Figures 4-7). Telescopic rods, such as Fassier-Duval rods, elongate with bone growth, reducing the need for repeated surgeries in growing children. Spinal fusion or instrumentation may be required for severe scoliosis or kyphosis [57].

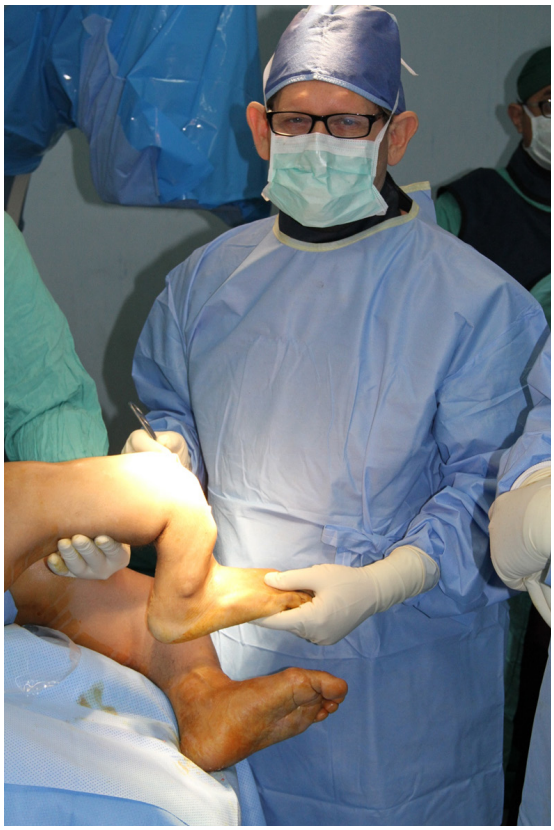

Figure 1: Bone deformity secondary to osteogenesis imperfecta.

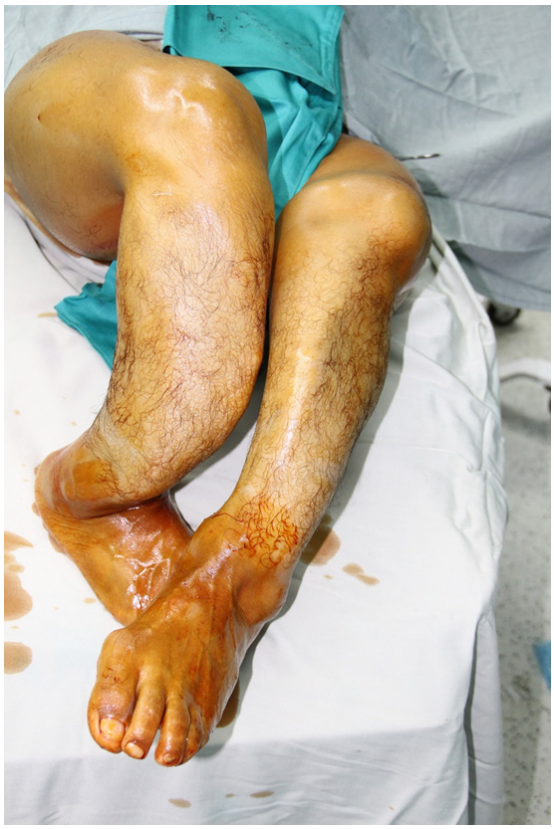

Figure 2: Bilateral lower extremity deformity due to Osteogenesis Imperfecta (OI).

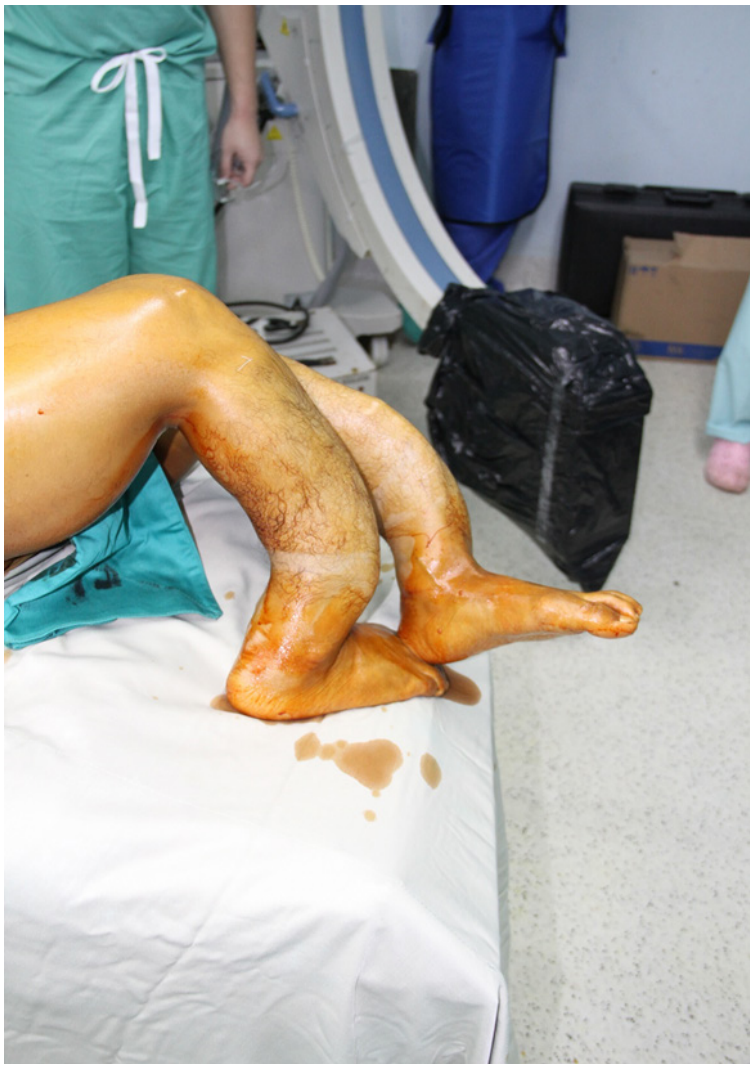

Figure 3: Bilateral lower extremity deformity due to Osteogenesis Imperfecta (OI).

Figure 4: Placement of guidewire for intramedullary rod.

Figure 5: Osteotomy of tibia.

Figure 6: Surgical manipulation of tibia into appropriate position.

Figure 7: Placement of tibial transfixing screw.

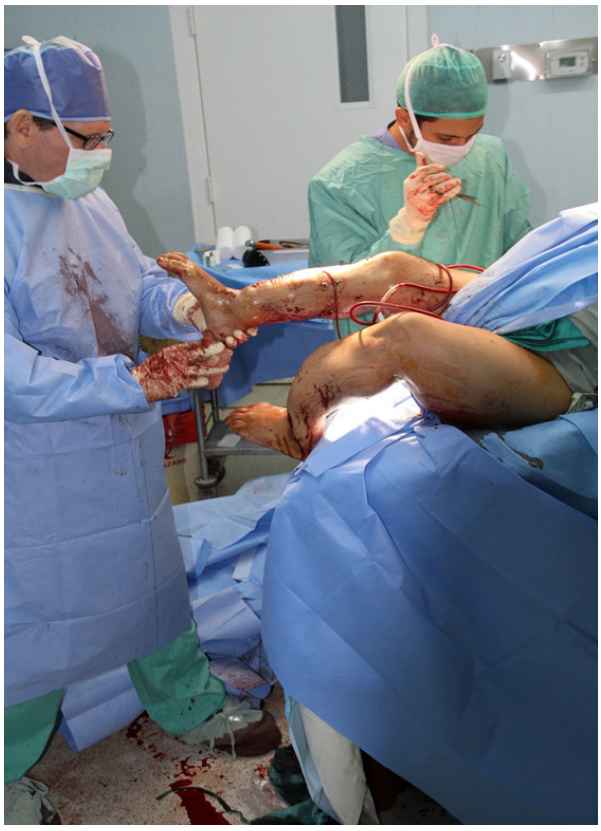

Figure 8: Right tibia and fibula surgical correction of the bone deformity.

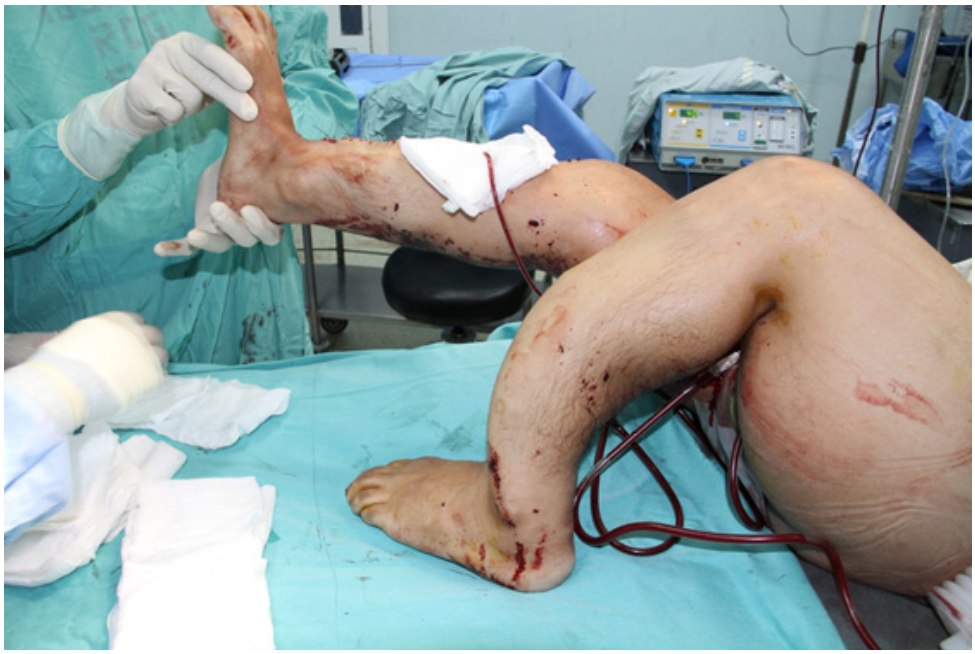

Figure 9: Right tibia and fibula surgical correction of bone deformity.

In addition to the interventions to combat signs, symptoms, and underlying causes of osteogenesis imperfecta, routine preventive care and intentional nutritional strategies can promote health and are important in osteogenesis imperfecta. For instance, because bone health relies on calcium and vitamin D, dietary intake of these nutrients is important in osteogenesis imperfecta, as is maintaining a healthy weight through a balanced diet so that excessive strain is not placed on fragile bones [30].

A multidisciplinary team should develop a tailored treatment approach individualized to each patient with osteogenesis imperfecta. In addition to primary care physicians, surgeons, nutritionists, and endocrinologists, physiatrists can support mobility and motor functioning and help to implement appropriate assistive devices.

CONCLUSION

Osteogenesis imperfecta predisposes individuals to fractures and skeletal complications of varying severity. Effective management requires a multidisciplinary approach that incorporates preventive care strategies coupled with pharmacological treatments, physical therapy and potentially surgical interventions. Emerging gene therapies may address the underlying genetic causes of the disorder, and research is underway to minimize the impact of defective collagen via therapies that target RNA [22,58].

CONFLICT OF INTEREST

There are no conflicts of interest associated with this manuscript.

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