Osteogenesis imperfecta is caused by qualitative or quantitative defects in type I collagen. Although often considered a disease with primarily pediatric manifestations, more than 25% of lifetime fractures are reported to occur in adulthood. General care of adults with osteogenesis imperfecta involves measures to preserve bone density, regular monitoring of hearing and dentition, and maintenance of muscle strength through physical therapy. Surgical stabilization of fractures in these patients can be challenging because of low bone mineral density, preexisting skeletal deformities, or obstruction by instrumentation from previous surgeries. Additionally, unique perioperative considerations exist when operatively managing fractures in patients with osteogenesis imperfecta. To date, there is little high-quality literature to help guide the optimal treatment of fractures in adult patients with osteogenesis imperfecta. [Orthopedics. 2017; 40(1):e17-e22.]

Osteogenesis imperfecta, also known as “brittle bone disease,” is a genetic disorder that affects type I collagen.1,2 Worldwide, osteogenesis imperfecta affects approximately 1 of every 20,000 births.3 In the United States, it affects between 25,000 and 50,000 individuals and is classified as an orphan disease (ie, a disease that affects fewer than 200,000 individuals nationwide).4 Osteogenesis imperfecta is the result of qualitative or quantitative defects in type I collagen that alter the microstructure of the bony skeleton, resulting in decreased bone density and strength. Although the severity of osteogenesis imperfecta depends on the specific mutation inherited by an individual, all patients are at an increased risk of bone fractures throughout life.5

Although most classically associated with skeletal fragility, osteogenesis imperfecta is a systemic disease that results in several manifestations. Type I collagen, although prominent in bone, is ubiquitous throughout the body; defects in its production and structure can profoundly affect the phenotype of affected individuals. Blue or grey sclera and ligamentous laxity are common manifestations of the disease.1 Dentinogenesis imperfecta can lead to the improper development of teeth, resulting in frequent physical damage and accelerated decay. Approximately half of individuals with osteogenesis imperfecta experience mixed conductive and sensorineural hearing loss by age 50.6 Patients with osteogenesis imperfecta can also have an increased risk of hernias, heart valve prolapse, and spinal deformities.2,7

The consequences of osteogenesis imperfecta can be devastating. In its most severe forms, multiple fractures in utero can expose fetal organs to trauma and interrupt lung development, resulting in early death. More commonly, patients with less severe forms of osteogenesis imperfecta sustain multiple fractures in the developing skeleton during childhood. This can lead to reduced height and decreased mobility.2 Complications from spinal struc-
tural abnormalities such as kyphoscoliosis and basilar invagination can cause respiratory insufficiency and are frequently encountered. Chronic pain from ligamentous laxity and multiple operative interventions can also reduce quality of life for affected individuals.

Etiology and Classification

Although it was once thought that osteogenesis imperfecta was primarily due to abnormalities in the COL1A1 and COL1A2 genes encoding type I collagen, it has been shown that some patients with osteogenesis imperfecta do not possess mutations in either of these genes. More accurately, osteogenesis imperfecta is a heterogeneous set of disorders that leads to defective or inadequate type I collagen. Inadequate production, defective post-translational modification, improper folding, and disrupted intracellular transport of collagen and/or its associated proteins can all lead to the osteogenesis imperfecta phenotype. Although autosomal dominant osteogenesis imperfecta primarily affects the quantity and quality of type I collagen directly, autosomal recessive osteogenesis imperfecta typically affects cofactors that normally interact with type I collagen.

In 1979, the Australian physician David Sillence proposed a classification system for osteogenesis imperfecta. The Sillence classification, which is still used today, originally subdivided osteogenesis imperfecta into 4 subgroups by radiographic, clinical, and genetic criteria. This classification has since been expanded, ultimately reaching 8 subgroups by 2007 to better account for the phenotypic and genetic differences between affected individuals (Table). As the molecular and genetic basis of osteogenesis imperfecta is better understood, the classification of osteogenesis imperfecta is likely to further expand.

Types I–IV are the result of direct mutations to the COL1A1 or COL1A2 genes and follow an autosomal dominant inheritance pattern. Type I osteogenesis imperfecta is caused by a nonsense mutation in the COL1A1 gene, resulting in the synthesis of half of the normal amount of type I collagen. It typically presents with mild deformity, and individuals exhibit normal or near-normal height, minimal skeletal deformity, and blue sclerae. Types II–IV are caused by glycine substitutions or splice site mutations in either COL1A1 or COL1A2, but their presentations differ dramatically. Type II osteogenesis imperfecta is usually lethal perinatally and is characterized by multiple long bone and rib fractures at birth, very low bone density, and dark sclerae. Type III osteogenesis imperfecta presents with severe skeletal deformity and is characterized by scoliosis, severe deficiencies in height, and dentinogenesis imperfecta. Type IV osteogenesis imperfecta is similar to type III in presentation, but is less severe. The underlying mutations in types V and VI are unclear; both present with moderate to severe skeletal deformity characterized by decreased height, an increased risk of fracture, white sclerae, and the absence of dentinogenesis imperfecta. Type VII, which presents like types V and VI, results from decreased expression of the CRTAP gene, whose gene product interacts with collagen. Type VIII is a severe form of the disease characterized by mutations in the LEPRE1 gene; it is often fatal perinatally.

Management of Osteogenesis Imperfecta in Adults

Management of fractures in adults with osteogenesis imperfecta is associated with unique challenges and employs a wide range of techniques, including casting, intramedullary fixation, and open reduction and internal fixation. Although surgical realignment and intramedullary stabilization improves mobility in pediatric patients with osteogenesis imperfecta, it does not eliminate the risk of subsequent fractures in adult patients with osteogenesis imperfecta, especially in those with more severe phenotypes. Patients often undergo multiple surgical procedures and may report bone pain, reduced mobility, and ligamentous laxity.

A survey of the musculoskeletal manifestations of osteogenesis imperfecta in 111 adults revealed that more than 25% of lifetime fractures occurred in adulthood. Patients also reported arthritis, joint instability, back pain, scoliosis, tendon ruptures, and complex regional pain syndrome. Of those surveyed, 15% reported that they required assistance with light physical tasks. Overall, 61% of patients reported that their overall health was good or excellent.
The first goal of treatment for adults with osteogenesis imperfecta involves preserving bone density, often through vitamin D and calcium supplementation, with regular monitoring of hearing and dentition and maintenance of muscle strength through physical therapy.² Prophylactic supplementation consisting of 500 to 1000 mg of calcium and 400 to 800 IU of vitamin D is recommended to aid in preserving bone density.¹² Terapeptide treatment for adults with less severe, type I osteogenesis imperfecta results in increased hip and spine bone mineral density, vertebral volumetric bone density, and estimated vertebral strength.¹³

Because they have been shown to improve bone density in patients with structural bone abnormalities, bisphosphonates are commonly prescribed to patients with osteogenesis imperfecta. Interestingly, however, data proving the reduction of the fracture rate in this population are limited.¹⁴ Shapiro and Germain-Lee¹⁵ showed that although bone mineral density increased in the hip and lumbar spine, an analysis of 5-year fracture rates revealed no difference compared with patients not receiving bisphosphonate therapy. The authors of this study questioned whether bisphosphonates are indicated for all patients with osteogenesis imperfecta. Additionally, there are concerns that high cumulative doses of bisphosphonates may impair bone healing and repair.¹⁶ Treatment with growth hormone may increase muscle mass and linear growth in children with osteogenesis imperfecta.¹⁷ Some initial studies have suggested that the use of the combination of bisphosphonate and growth hormone therapy may be of some benefit to osteogenesis imperfecta patients.¹⁸ However, because of osteogenesis imperfecta’s nature as a genetic disease, pharmacological therapy is currently unable to adequately target the underlying defects in affected patients. In the future, advanced molecular techniques and gene therapy may yield more definitive solutions for osteogenesis imperfecta.

## Long Bone Fractures

Long bones of patients with osteogenesis imperfecta are susceptible to higher bending moments and altered mechanical properties due to preexisting deformity as well as long-term bisphosphonate treatment (Figure).¹⁹ Intramedullary fixation is the primary treatment for long bone fractures in osteogenesis imperfecta because it minimizes stress concentrations that predispose the bone to periprosthetic fracture.²⁰ However, intramedullary fixation does not uniformly result in adequate union of fractures or osteotomies in patients with osteogenesis imperfecta. This is particularly true as patients age and body weight and bone length increase while the intramedullary diameter remains small, allowing for a relatively small intramedullary implant diameter. This may result in inadequate stability and subsequent nonunion.²⁰ Nonunion has been reported in up to 24% of fractures and 52% of osteotomies.²¹ Delayed union or nonunion can result in re-fracture and angular deformity.²¹ Bisphosphonate treatment and inadequate rotational stability associated with intramedullary implants are implicated in delayed union, particularly among adolescents and adults.²¹ Cho et al²⁰ reported 100% fracture healing after intramedullary fixation of long bones augmented with a long plate and unicortical screws. Once healing of the nonunion site occurs, the locking plate should be removed; however, Cho et al reported that plate removal was generally delayed until another surgical procedure was performed. They also noted that although their augmentation technique was effective, there was inherent risk of fracture around the screw holes of the plate, given the stress concentration around these sites.

Puvanesarajah et al²² reported a 92% (n=12) healing rate in long fracture non-unions after treatment with intramedullary fixation augmented with compressed sandwich allograft cortical struts. One patient required additional allograft struts and a new intramedullary rod because of re-fracture, which ultimately healed. Radius, femur, humerus, and fibula allograft bone were used. The allograft bone was selected to provide adequate mechanical support and to minimize prominence. The allograft bone was halved and contoured to the nonunion site and was fixed to the donor site with mini fragment screws, cerclage wires, or cerclage nonabsorbable suture.²²

## Femoral Neck Fractures

In patients with osteogenesis imperfecta, the femur is the site that most commonly requires surgical intervention for fracture or malalignment.²³ However, fractures of the femoral neck are relatively uncommon in patients with osteogenesis imperfecta.¹⁹,²³,²⁴ Surgical stabilization of femoral neck fractures is challenging because of low bone mineral density or obstruction by hardware from previous

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**Figure:** Anteroposterior radiograph of a femoral shaft fracture after applying temporary splint immobilization for a 19-year-old woman. She had type III osteogenesis imperfecta and a history of multiple long bone fractures as well as scoliosis for which she had had multiple long bone and spine surgeries. She lost her balance and fell while she was maneuvering into her wheelchair, which resulted in a right subtrochanteric femur fracture.
fracture fixation, specifically the presence of femoral intramedullary hardware that was used for stabilization of the femoral shaft in pediatric patients with osteogenesis imperfecta.19

Chow et al24 reported the management of femoral neck fractures in 2 adults with osteogenesis imperfecta. The first case involved a 22-year-old woman who sustained a femoral neck fracture and a supracondylar fracture of the distal femur. She had a proximal femoral osteotomy fixed with a dynamic hip screw construct when she was 12 years old. The fracture occurred at the tip of the lag screw of the dynamic hip screw. Prior to removal of the lag screw, a cannulated screw was used to stabilize the fracture. Once the lag screw was removed, a second screw was inserted, resulting in acceptable stability. The supracondylar fracture of the left femur was stabilized with crossed Kirschner wire fixation. She was immobilized in a hip spica cast for 6 weeks, and both fractures had healed 8 weeks postoperatively. The second patient was 21 years old and had sustained a femoral neck fracture and bilateral supracondylar fractures of both femurs. An intramedullary Rush rod was present in the left femur from a previous modified Sofield-Millar operation. The femoral neck fracture was fixed in situ with cannulated cancellous screws and the supracondylar fractures were fixed with crossed Kirschner wires. The patient was immobilized in a hip spica cast. Three days postoperatively, imaging revealed that the femoral neck fracture had displaced, resulting in return to the operating room for open reduction and internal fixation with additional cancellous screws. The fracture had healed at 3 months without deformation.24

Because of their poor quality bone, limited size and therefore rigidity of osteosynthesis implants, and often limited ability to adequately stabilize fractures with internal fixation alone, it is important to augment any internal fixation with supplemental spica cast immobilization when treating femur fractures in adults with osteogenesis imperfecta. Although normal size adults may be poorly tolerant of spica cast immobilization, patients with osteogenesis imperfecta are much smaller and the spica cast burden is often better tolerated.

**Acetabular Fractures**

Fractures of the acetabulum are typically due to high-energy mechanisms; however, in patients with osteogenesis imperfecta who present with pelvic or hip pain, there should be a high index of suspicion for fractures of the acetabulum regardless of mechanism. Acetabular surgery in adults with osteogenesis imperfecta is challenging because of the potential for preexisting acetabular protrusio, osteopenia, compromised tissue quality, and a predisposition to excessive bleeding.25 Darmanis and Bircher25 reported 2 cases in which they encountered significant blood loss (≥1.5 L), friable tissue, and the inability to obtain fixation with a screw through the quadrilateral plate because it had been thinned secondary to acetabular protrusio. In both cases, they used standard hardware but had to adapt their technique to accommodate the acetabular irregularities that existed secondary to osteogenesis imperfecta.25 In the first case, the quadrilateral plate was thin secondary to acetabular protrusio. Therefore, a screw could not be successfully passed through it into the anterior wall without compromising the hip joint. Rather, the screw was passed transversely from the ilium to the anterior wall. In the second case, the quadrilateral plate was again thin secondary to acetabular protrusio. Therefore, a 4-hole plate was placed over the large pelvic brim plate to support the thin quadrilateral plate and the posterior column fracture.

**Spine Fractures**

In addition to being predisposed to developing kyphotic scoliosis, patients with osteogenesis imperfecta are predisposed to fractures of the spine because of their ligamentous laxity and decreased bone mineral density. Hangman fractures of the C2 vertebrae have been reported in the literature among patients with osteogenesis imperfecta.26 Type I and II hangman fractures in patients with no neurological deficits have been successfully managed conservatively with a rigid cervical collar.

Wakao et al27 reported a case of a 29-year-old man who sustained an L1 burst fracture after diving head first into a river. After 3 months of conservative management in a body cast, the patient subsequently developed a painful kyphotic deformity at the site of the fracture. The authors used an anterior-posterior surgery to correct the deformity and place instrumentation and bone graft with iliac crest autograft and allograft around the fracture to obtain a circumferential fusion. At the 2-year follow-up, both pain and functional outcome scores had improved.27

The diminished bone mineral density in patients with osteogenesis imperfecta predisposes them to vertebral compression fractures similar to those in patients with osteoporosis.28 Reports regarding the efficacy and safety of vertebroplasty have not been consistent. Kasó et al29 reported significant pain relief associated with vertebroplasty, whereas Vasconcelos et al,30 Abdul-Jalil et al,30 and Tozzi et al31 reported significant complications associated with this procedure, including pulmonary embolism resulting from cement in the pulmonary arteries and transient arterial hypotension during the injection of cement.30,31 Leng et al32 reported a case of cervical spine compression at C7 in a 46-year-old man after a fall. The patient was managed nonoperatively in a rigid cervical collar. A repeat computed tomography scan after 3 months of treatment revealed stable alignment.

**Perioperative and Postoperative Management**

Bleeding diathesis is present in 10% to 30% of patients with osteogenesis imperfecta as a result of collagen defects that
lead to increased capillary fragility, friable tissues, and compromised collagen-induced platelet aggregation.\textsuperscript{33,34} The extent of bleeding that will occur during surgical procedures in patients with osteogenesis imperfecta is often unpredictable, even if coagulation studies and bleeding times are normal.\textsuperscript{35} The use of Cell Saver (Haemonetics, Pittsburgh, Pennsylvania) should be considered in cases for which long operative time and extensive exposure are required.\textsuperscript{25} A careful preoperative evaluation with special attention to lung function is essential in types III and IV.\textsuperscript{12} Additionally, many patients with osteogenesis imperfecta may have an elevated temperature throughout the operation; however, malignant hyperthermia is not a condition known to be associated with osteogenesis imperfecta.\textsuperscript{36} Stabilization of the cervical spine by anesthesia is critical during intubation and throughout the case because of the possibility of instability and the potential for preexisting basilar invagination in these patients.\textsuperscript{36}

Postoperative pain management can be challenging owing to the opioid tolerance that has developed because of long-term use of narcotic pain medication.\textsuperscript{37} After surgery, prolonged immobilization should be avoided and early rehabilitation should be initiated to avoid further stiffness and muscle atrophy.\textsuperscript{12}

\textbf{Conclusion}

Osteogenesis imperfecta is caused by qualitative or quantitative defects in type I collagen. Osteogenesis imperfecta is a lifelong disease with unique considerations for the adult patient. General care of adults with osteogenesis imperfecta involves measures to preserve bone density, including vitamin D and calcium supplementation; regular monitoring of hearing and dentition; and maintenance of muscle strength through physical therapy. Bisphosphonate therapy plays a role in preserving bone mineral density; however, there are limited data regarding its ability to decrease fracture rates in osteogenesis imperfecta. Surgical stabilization of fractures is difficult because poor bone quality limits fixation techniques that can achieve a stable construct. Prior hardware from childhood injuries and stabilization procedures also limits the approach to fixation. Unique perioperative considerations exist, including blood loss, respiratory function, and spine stabilization during induction, when operatively managing fracture in patients with osteogenesis imperfecta. Ultimately, evidence-based studies on fracture management in adults with osteogenesis imperfecta are limited, and patients should be evaluated on a case-by-case basis by multidisciplinary teams to help maximize short- and long-term outcomes.

\textbf{References}


