Osteogenesis Imperfecta

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Abstract

Osteogenesis imperfecta (OI) is a genetically determined disorder of connective tissue characterized by bone fragility. The disease state encompasses a phenotypically and genotypically heterogeneous group of inherited disorders that result from mutations in the genes that code for type I collagen. The disorder is manifest in tissues in which the principal matrix protein is type I collagen (mainly bone, dentin, sclerae, and ligaments). Musculoskeletal manifestations are variable in severity along a continuum ranging from perinatal lethal forms with crumpled bones to moderate forms with deformity and propensity to fracture to clinically silent forms with subtle osteopenia and no deformity. The differential diagnosis includes other entities with multiple fractures, deformities, and osteopenia. Classification is based on the timing of fractures or on multiple clinical, genetic, and radiologic features. Molecular genetic studies have identified more than 150 mutations of the COL1A1 and COL1A2 genes, which encode for type I procollagen. Various systemic treatments have been attempted; however, these interventions have been ineffective or inconclusive or are still experimental. Gene therapy has the potential to increase the synthesis of type I collagen in mild variants and to correct mutations in severe variants, but there are a great number of technical difficulties to overcome. The goals of treatment of OI are to maximize function, minimize deformity and disability, maintain comfort, achieve relative independence in activities of daily living, and enhance social integration. Attainment of these goals requires a team approach to tailor treatment needs to the severity of the disease and the age of the patient. Nonoperative management is the mainstay of orthopaedic treatment, with the goals of preventing and treating fractures and enhancing locomotion. Operative intervention is indicated for recurrent fractures or deformity that impairs function.

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Osteogenesis imperfecta (OI) is a genetically determined disorder of connective tissue characterized by bone fragility. The disease state encompasses a phenotypically and genotypically heterogeneous group of inherited disorders resulting from mutations in genes coding for type I collagen. Osteogenesis imperfecta has been grouped clinically with other heritable disorders of connective tissue, including Ehlers-Danlos syndrome, Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, cutis laxa, pseudoxanthoma elasticum, fibrodysplasia ossificans progressiva, and the chondrodysplasias, but molecular studies are beginning to allow more precise delineation. Osteogenesis imperfecta is most closely related to type VIIA and type VIIB Ehlers-Danlos syndrome, which also result from mutations in type I collagen genes.

The clinical disease state is manifested in tissues in which the principal matrix protein is type I collagen (mainly bone, dentin, sclerae, and ligaments). The phenotypic manifestations are variable in severity, ranging from perinatal lethal forms with crumpled bones and severe deformity to clinically silent forms with subtle osteopenia and no deformity (Table 1). The various classifications of OI will be discussed in the "Classifications" section, but in general, clinical subtypes represent a series of syndromes related to classes of molecular defects, each with a reasonably well-defined phenotypic pattern.

Osteogenesis imperfecta is ubiquitous in ethnogeographic distribution. The prevalence of OI is approximately 16 cases per million index patients. Sillence type I OI is by far the most common clinical subtype except in southern Africa, where type III is more common. The incidence of the mild type I (tarda) form is estimated at 3 to 5 per 100,000; that of the severe deforming type III form, 1 to 2 per

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Table 1
Clinical Features and Classification of Osteogenesis Imperfecta

Sillence Type[13]	Shapiro Type[12]	Type	Features	Inheritance
I	Tarda B	Mild form	Blue sclerae, normal teeth (Sillence subtype IA) or dentinogenesis imperfecta (Sillence subtype IB), mild bone fragility, fractures after walking, minimal deformity	Autosomal dominant, new mutations
II	Congenita A	Lethal perinatal	Blue sclerae, stillborn or neonatal death, numerous intrauterine fractures, crumpled long bones, severe deformity	Autosomal recessive, new mutations, mosaicism
III	Congenita B, tarda A	Severe deforming	Normal sclerae, dentinogenesis imperfecta, often fractures at birth, frequent fractures, frequent deformity, short stature, spine deformity	Autosomal recessive, new mutations, mosaicism
IV	. . .	Intermediate form	Normal sclerae, normal teeth (Sillence subtype IVA) or dentinogenesis imperfecta (Sillence subtype IVB), moderate bone fragility, moderate deformity, short stature, phenotypic variability	Autosomal dominant

100,000 births; that of the lethal perinatal type II (congenita) form, 1 per 40,000 to 60,000 births. The intermediate type IV form is rare, with an unknown frequency.[1,2]

The disease was first described scientifically by Ekman in 1788, who detailed involvement in four generations of a family in Sweden for his doctoral thesis. Since then, more than 40 different names and eponyms have been used, including mollities ossium, fragilitas ossium, osteopsathyrosis idiopathica, osteomalacia congenita, osteoporosis fetalis, Eddome syndrome, van der Hoeve syndrome, Vrolik disease, and Lobstein disease.[1,2] The term "osteogenesis imperfecta" was first used by Vrolik in 1849 when describing the pathologic features of involved bone.

The disease likely dates back to antiquity; an Egyptian mummy from 1000 BC has been described as having a wormian bone mosaic of the skull, amber-colored teeth, and severely bowed legs. It is speculated that Ivar the Boneless, mastermind behind the Scandinavian invasion of England in the 9th century, had OI. Legend has it that he was unable to walk and was carried into battle on a shield. Unfortunately, his skeleton is not available, as it was exhumed and burned by William the Conqueror.[1]

Basic clinical and genetic studies have identified the phenotypic characteristics of OI, leading to the development of classification schemes and management strategies. More recently, biochemical and molecular genetic studies have characterized many of the protein defects and collagen mutations in OI, elucidating the genotypic characteristics of this disease. This article reviews the clinical manifestations, diagnosis, classification, molecular basis, and management of OI.

Clinical Manifestations

Musculoskeletal System

The musculoskeletal features of OI are variable in their extent and severity, depending on the clinical subtype and reflecting the underlying genotypic heterogeneity. Gross skeletal features include short stature (with dwarfing in severe forms), kyphoscoliosis, pectus excavatum, and trefoil-shaped pelvis with protrusio acetabuli. The skull is often misshapen, with a broad forehead, flattened posterior cranium, overhanging occiput, bulging calvaria, and triangular facial shape. Depending on the severity of disease, there may be marked long-bone deformity with anterior bowing of the humerus, tibia, and fibula and lateral bowing of the femur, radius, and ulna.

The overall incidence of spine deformity in OI is approximately 60%, ranging from 90% for congenita forms to 10% to 40% for tarda forms.[3] Thoracic scoliosis is the most common deformity and arises secondary to osteoporosis, compression fractures, and ligamentous laxity. The deformity of the thorax associated with multiple rib fractures, spinal deformity, molding of

the soft thorax, and pectus excavatum or carinatum can be sufficiently severe to compromise respiratory function. Ligamentous laxity results in hypermobile joints with joint dislocations, patellar tendon ruptures, and pes planus. There is often a secondary muscular hypotonia and underdevelopment related to tendon or ligament anomalies and reduced activity.

The hallmark of OI is bone fragility. As with the other phenotypic features of OI, the propensity to fracture is extremely variable, with manifestations ranging from innumerable fractures in utero and at birth to their virtual absence in an adult. The timing and number of fractures is included in some classification schemes. In general, the more severe forms of OI are characterized by earlier and more numerous fractures. These fractures often occur after minor trauma and can present with little pain. Fractures generally heal with abundant callus; however, the reparative bone is also abnormal, and fractures frequently lead to malunion and pseudarthroses with resultant long-bone deformity. The incidence of fractures decreases after puberty and rises again in women after menopause and in men after age 60.

The radiographic features of OI are also proportional to disease severity. The radiologic hallmark of OI is diffuse osteopenia associated with multiple fractures and deformities. Generalized osteopenia is seen in almost every case, and there is often equal involvement of the appendicular and axial skeletons.

The long bones of the lower extremities are usually more severely affected than those of the upper extremities. The long bones most often appear slender; however, they may show focal areas of thickened cortices secondary to callus buttressing or telescoping of fractures. The metaphyses of the long bones can be trumpet-shaped and cystic in appearance. In severe cases, "popcorn" calcifications appear in childhood in the metaphyseal/epiphyseal regions as displaced, fragmented physeal cartilage undergoes endochondral ossification. These calcifications commonly resolve after skeletal maturity, when all cartilage is transformed to bone.

The vertebrae in OI often demonstrate flattening or are biconcave secondary to multiple microfractures. Kyphoscoliosis often results.

The skull is characterized by wormian bones, as first described by the Danish anatomist Olaus Wormius in 1643. This appearance represents small, independent areas of primary ossification within membranous bones arranged in a mosaic pattern (Fig. 1).

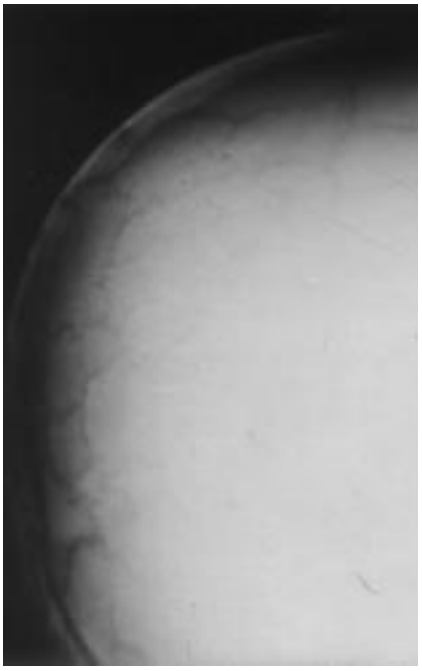

Fig. 1 Anteroposterior (AP) skull radiograph demonstrates wormian bone mosaic pattern.

Hyperplastic callus formation is rare but can occur in patients with OI. It often presents as pain, an enlarging mass, and erythema, and can be difficult to distinguish from osteosarcoma radiographically, clinically, and even histologically.

The histopathologic features of OI also vary depending on disease severity. Overall, there is a generalized decrease in bone tissue, with the bone structure demonstrating a mixture of woven and lamellar patterns. The histologic appearance of bone in OI patients follows the normal developmental and structural pattern but rarely achieves the fully compacted lamellar state. The more severe the involvement, the more immature the structural pattern. In more severe forms of OI, the bone appears histologically as a woven bone matrix devoid of any organized lamellar pattern (Fig. 2). There are plump osteoblasts crowded along prominent osteoid seams, large oval osteocytes surrounded by small amounts of matrix, and morphologically normal osteoclasts.

Histologic sections from patients with less severe OI show a definite tendency to lamellar bone formation (Fig. 2). The lamellation and osteon formation can be rudimentary, partially compacted, or fully compacted in localized areas. Osteoid seams are prominent, and there is hypercellularity, with larger than normal osteocytes and osteoblasts in the areas of woven bone. There is a correlation between the degree of osteonal maturity and bone strength as indicated by ambulatory status.

The articular cartilage appears normal. The physis often shows disorganization of the proliferative and hypertrophic zones with increased permeation of cartilage by metaphyseal blood vessels. The metaphysis is composed of a scanty, woven primary spongiosa. There is increased bone turnover as defined by tetracycline-labeling studies. Callus bone is largely woven. Ultrastructural studies show a predominantly random

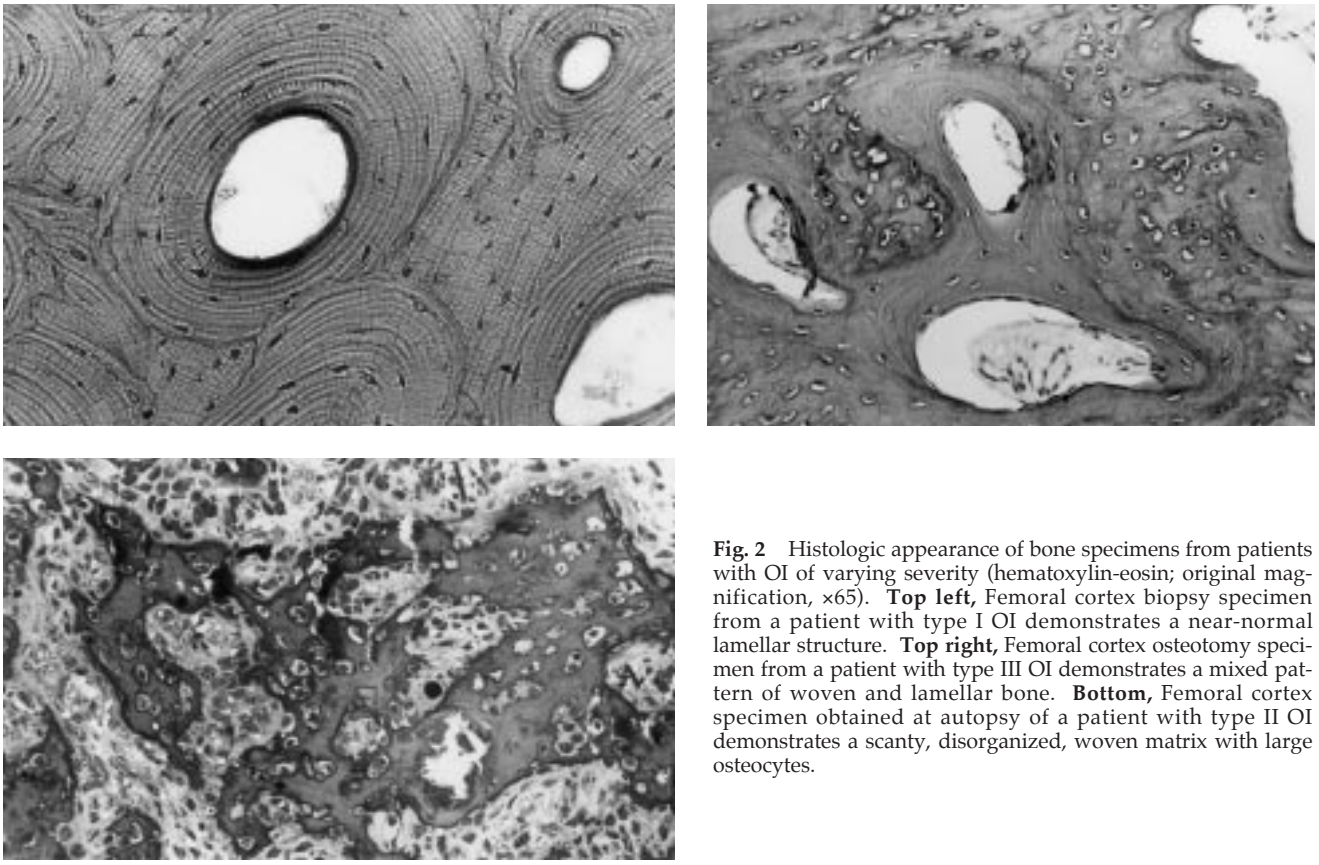

Fig. 2 Histologic appearance of bone specimens from patients with OI of varying severity (hematoxylin-eosin; original magnification, ×65). **Top left,** Femoral cortex biopsy specimen from a patient with type I OI demonstrates a near-normal lamellar structure. **Top right,** Femoral cortex osteotomy specimen from a patient with type III OI demonstrates a mixed pattern of woven and lamellar bone. **Bottom,** Femoral cortex specimen obtained at autopsy of a patient with type II OI demonstrates a scanty, disorganized, woven matrix with large osteocytes.

arrangement of thinner collagen fibers consistent with the light-microscopic woven pattern.[4,5]

Other Systems

The effects of OI are not limited to bone, but also involve tissues in which the primary matrix protein is type I collagen (dentin, sclerae, skin, and ligaments). System involvement (e.g., otologic, neurologic, and respiratory) is secondary to deformity and to primary metabolic abnormalities.

Dentinogenesis imperfecta is characterized by soft, translucent brownish teeth. The teeth are affected in a nonuniform manner, with involvement usually greater in the primary teeth than in the secondary teeth. The enamel wears easily, and the teeth are carious, shortened, and susceptible to cracking. On x-ray films, the crowns are bulbous, and there is obliteration of pulp chambers. About 30% of individuals with all types of OI have significant dental involvement. The Sillence classification scheme subclassifies type I and type IV OI on the basis of the presence or absence of dentinogenesis imperfecta. Dental treatment includes crowning, dentures, and intraosseous implants.

The blue sclerae in OI are the result of increased corneal translucency (secondary to abnormal collagen), which reveals the underlying uveal pigment and blood vessels. This color changes with age, becoming more grayish in adulthood. The pericorneal region of the sclera is often white and opaque, resulting in a "Saturn's ring" appearance, and there may be opacities in the periphery of the cornea, giving an arcus juvenilis appearance. Hypermetropia is common.

The skin in OI is often thin, translucent, and easily distensible, resembling the atrophic skin of elderly patients owing to collagen insufficiency of the dermal layer. Surgical scars commonly heal with widening and prominence. Ligamentous laxity is a characteristic feature of OI. Pes planus is the principal clinical manifestation, but other disorders of hyperlaxity, such as subluxating patellae and dysplastic hips, are occasionally seen. There is increased vascular fragility, and a minority of patients demonstrate nonprogressive aortic root dilatation. Valvular disease, in particular mitral valve prolapse, is much less common than in Marfan syndrome, but has been reported.[6]

The onset of hearing loss in OI begins in adolescence and becomes problematic for nearly 50% of affected adults. It is seen primarily in the type I benign autosomal dominant variant. Hearing loss can be conductive, sensorineural, or mixed. The extent of deafness is variable; however, loss in the high-frequency range is characteristic. Treatment usually involves prosthetic stapedial footplate replacement or stapedectomy. Other otologic findings include recurrent middle ear infections and sinusitis, tinnitus from stapedial fixation, vertigo from labyrinthine involvement, and speech delay.

Intelligence is usually normal. Low-pressure hydrocephalus can be seen in some severe forms of OI. The anterior fontanel remains open, and there is general dilation of the ventricles with cortical atrophy. This process is usually self-limiting and does not require shunting. Basilar impression occurs predominantly in Sillence type III and type IV OI. There is brainstem and spinal cord compression at the foramen magnum, resulting in progressive cerebellar disturbance and lower cranial nerve dysfunction; this may require cranial decompression, which has had variable results.

Metabolic abnormalities, present to a variable extent in patients with OI, are characterized by hypermetabolism, heat intolerance, elevated body temperature, increased sweating, and resting tachypnea and tachycardia. These findings are generally attributed to high metabolic activity and turnover of the connective tissue cells. Hyperthermia can occur during anesthesia; rarely, true malignant hyperthermia may occur. There is evidence of uncoupling of oxidative phosphorylation in leukocytes and defects in platelet adhesion and clot retraction in patients with OI.[7,8]

Diagnosis

The diagnosis of OI is still based primarily on clinical and radiographic criteria. Fibroblast cell culture from skin biopsy specimens can now be used to detect collagen molecular abnormalities (discussed in the "Molecular Basis" section) in approximately 85% of patients with OI. The differential diagnosis of OI in infancy is relatively limited. Hypophosphatasia presents with multiple fractures, deformities, and osteopenia. Other disorders, such as achondrogenesis, achondroplasia, pyknodysostosis, rickets, Menkes syndrome, and homocystinuria, have their own distinguishing features.

Diagnosis in childhood and adolescence can be more difficult due to less severe involvement. The differential diagnosis includes leukemia, fibrous dysplasia, and idiopathic juvenile osteoporosis. Idiopathic juvenile osteoporosis is an extremely rare disorder with onset at puberty. It is characterized by generalized osteopenia and propensity to fracture. Spontaneous remission has been reported. It can be distinguished from OI by its onset in adolescence, the presence of normal sclerae and teeth, and a negative family history.

Hypophosphatasia resembles OI with blue sclerae, bowing of legs, and osteopenia; it can be differentiated from OI by abnormal laboratory findings such as the urine excretion product phosphoethanolamine and markedly decreased serum alkaline phosphatase levels. Homocystinuria is characterized by osteoporosis, biconcave vertebrae, and susceptibility to fracture; it can be differentiated from OI by a marfanoid habitus, ectopia lentis, and abnormal urinary metabolites.

The distinction between mild forms of OI and child abuse can be difficult, but is crucial to consider.[9] Both may present with a propensity to fracture without a clear history of definite trauma. Classically, abuse presents with multiple fractures in different stages of healing, posterior rib fractures, metaphyseal corner fractures, and skull fractures. Other signs of abuse include bruises, burns, and retinal hemorrhages.

Prenatal diagnosis of OI can be made on the basis of structural characteristics noted on fetal ultrasound, collagen molecular studies of cultured chorionic villus cells, or genetic linkage studies with the use of collagen markers.[10] Prenatal detection in pregnancies at risk for OI can provide valuable information for genetic counseling and obstetric management. Ideally, genetic counseling would provide information concerning the likely outcome of future pregnancies and the prognosis for individual affected children. In actuality, however, this is difficult because of the high incidence of spontaneous mutations and sporadic cases, the lack of diagnostic tests in the index case, and the lack of an accurate carrier test.

Ultrasonography can effectively screen fetuses for severe forms of OI, but it remains difficult to detect mild forms. Sillence type II OI can be recognized on ultrasound scans obtained before 20 weeks' gestation by assessing femoral length adjusted for gestational age, extent of mineralization, evidence of fractures, skull echogenicity, and thoracic abnormalities. Midtrimester ultrasonography is usually useful in detecting type III OI by depiction of intrauterine fractures and deformity. Advances in transvaginal ultrasound may provide a means of first-trimester prenatal diagnosis of severe forms of OI.

If a certain biochemical defect of collagen or a specific mutation has been identified in an affected parent or sibling, prenatal detection can be accomplished by screening fetal tissue for the presence of that

defect. This is performed by culturing chorionic villus cells and examining the electrophoretic properties of the collagen they produce. Amniotic fluid cells are, in general, not useful because most cells synthesize a variant of type I procollagen. Linkage studies performed with the use of collagen markers are currently the diagnostic investigation of choice for families with autosomal dominant OI, allowing genotyping of the fetus.[11]

Classifications

Clinical, radiographic, molecular, and genetic studies support the concept that OI is a syndrome with several variants related to classes of type I collagen mutations, each with a reasonably well-defined phenotypic pattern. As a result of the extensive phenotypic heterogeneity of OI, numerous classifications have been proposed to categorize clinical subtypes, provide a framework for understanding the natural history, and guide management.

Looser, in 1906, classified OI into two types on the basis of when the first fractures occurred: congenita (fractures at birth) and tarda (fractures after the perinatal period). He noted that the prognosis in the congenita type was poor, with a high mortality rate. Seedorff, in 1949, further subclassified OI tarda into gravis (fracture occurs within the first year of life) and levis (fracture occurs after the first year of life), noting that tarda gravis was associated with the development of severe deformities and disability.

Shapiro,[12] in 1985, revisited this concept, defining natural history and musculoskeletal prognosis on the basis of the time of initial fracture and the radiographic appearance of the bones at the time of initial fracture. Patients with the congenita form have intrauterine or birth fractures. Patients with the tarda form sustain fractures initially after birth. The congenita form of OI was subdivided into type A (crumpled femurs and ribs) and type B (normal bone contours with intrauterine/birth fractures). The tarda form was subdivided into type A (fractures before walking) and type B (fractures after walking). At follow-up in that study, patients in the congenita type A group had a mortality rate of 94%. Patients in the congenita type B group had a mortality rate of only 8%, with 59% eventually becoming wheelchair-bound and 33% being ambulatory. In the tarda type A group, 33% of patients were wheelchair-bound, and 67% were ambulatory. All patients in the tarda type B group were ambulatory.

The classification system currently used most widely was developed by Sillence in 1979 from a comprehensive survey of patients in Australia. The Sillence classification divides OI patients into four types on the basis of multiple clinical, genetic, and radiologic features (Table 1).[1,13,14] Type I OI is the mildest and most common form. Inheritance is autosomal dominant, although new mutations are frequent. Type I is subclassified into the more common type A (without dentinogenesis imperfecta) and the less common type B (with dentinogenesis imperfecta). The sclerae are blue, and the first fractures usually occur in the preschool years, after walking has begun. There is commonly absence of significant deformity; kyphoscoliosis is comparatively mild and uncommon; and stature is generally normal. Life expectancy is normal for patients with type IA OI and only marginally impaired for those with type IB. Socially, type I OI patients are scarcely distinguishable from the normal population, with most fully employed and living independently.

Type II OI (Fig. 3) is the lethal perinatal form. Many fetuses are

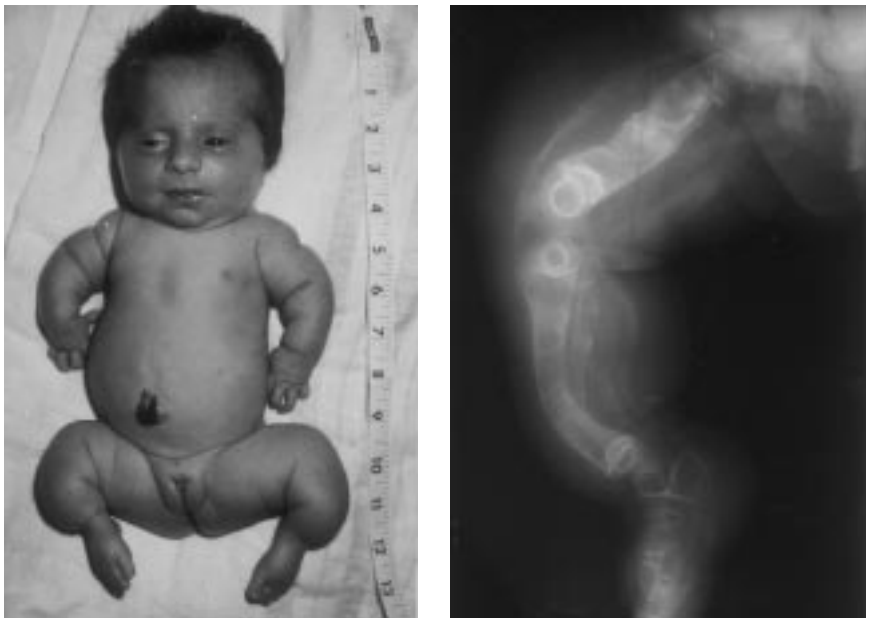

Fig. 3 **A,** Six-week-old neonate with lethal perinatal type II OI who died at 12 weeks due to respiratory failure. Features included blue sclerae, short stature, and short, deformed extremities. **B,** Lateral lower-extremity radiograph of another child with type II OI shows osteopenia, short crumpled femurs, multiple fractures, and deformity.

stillborn, and survivors are often born prematurely. The disorder is usually lethal within the first few weeks of life, but some affected infants survive for several months, and a few live for one or more years. Death is generally due to respiratory failure, intracranial hemorrhage, or brainstem compression. The sclerae tend to be blue or grayish. There are multiple intrauterine fractures, and the femurs, tibias, and ribs are short, broad, crumpled, and deformed. Inheritance was thought to be autosomal recessive; however, most cases appear to result from new dominant mutations in a proband of unaffected parents. Occasionally, unaffected parents have multiple affected children; this is thought to result from parental mosaicism or to be due to a rare autosomal recessive form.

Type III OI is the severe deforming form, with fractures generally present at birth (Fig. 4). The sclerae are generally normal in color. Frequent fractures and deformity are common, stature is typically severely shortened, and the spine is often deformed (Fig. 5). Respiratory complications and dentinogenesis imperfecta are common. Inheritance is thought to be autosomal recessive; however, new dominant mutations are common, and a rare autosomal dominant variety exists. Life expectancy is decreased, but affected individuals live into adulthood. Early mortality is due to respiratory illness, injury with intracranial hemorrhage, and basilar invagination.

Type IV OI is a moderately severe form with great phenotypic variation, but is usually intermediate in severity between type III and type I. This variant is infrequent, accounting for approximately 5% of cases. Sclerae are normal, short stature is variable, dentinogenesis imperfecta is common, and fractures and deformity are relatively common. Inheritance is autosomal dominant. Life expectancy can be decreased depending on disease severity; however, a large percentage of patients function independently well into adulthood.

The Sillence classification correlates with the congenita/tarda temporal-radiographic Shapiro groups. The congenita A group encompasses Sillence type II lethal perinatal patients; congenita B and tarda A are generally Sillence type III patients with progressive deformity; and tarda B represents the Sillence type I benign autosomal dominant patients (Table 1).

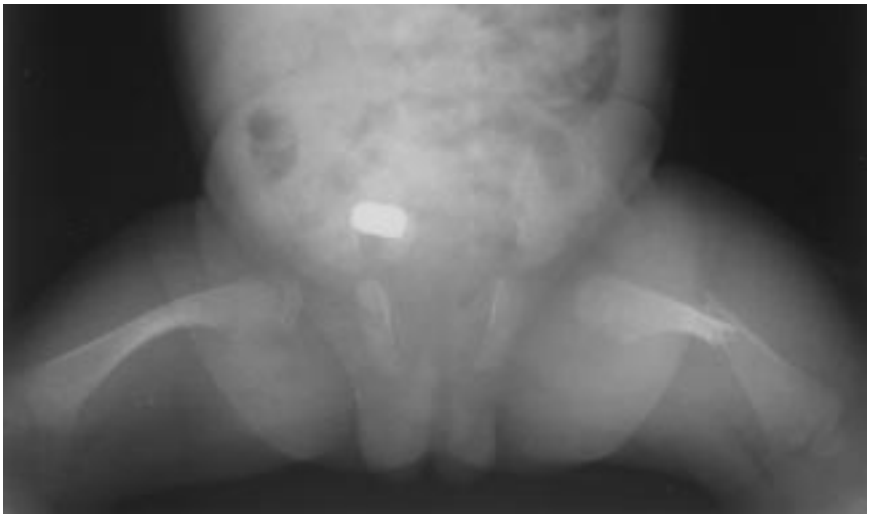

Fig. 4 Radiograph of a newborn with type III OI. Features include osteopenia and a fracture of the left femur.

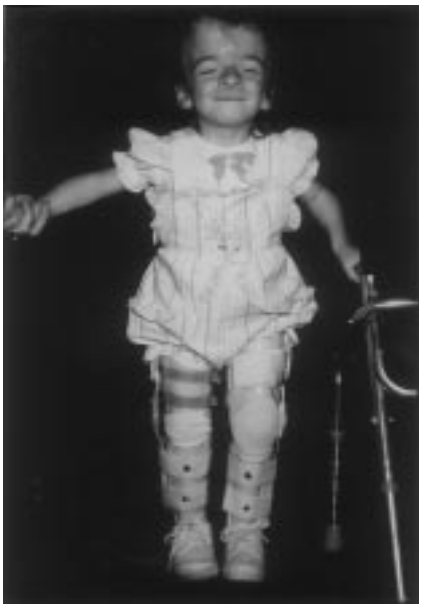

Fig. 5 Four-year-old child with type III OI. Features include a broad flattened forehead, short arms, and short stature. She has undergone osteotomies with intramedullary rodding of her lower extremities and ambulates with braces and a walker.

Molecular Basis

Studies examining the skin of patients with OI in the 1960s and 1970s gave the first clear indication of collagen abnormalities. Subsequently, skin fibroblast cell culture studies have confirmed that the cells of affected individuals produce either decreased amounts of collagen or defective collagen. Detailed biochemical investigations have demonstrated heterogeneity of type I collagen defects.

Recently, molecular biology studies have defined more than 150 specific gene mutations that result in OI, and investigations to characterize the mechanisms that translate these mutations into the various observed phenotypes are ongoing.[2,15-18]

Osteogenesis imperfecta is caused by mutations in the COL1A1 (18-kilobase [kb] size, located on the long arm of chromosome 17) and COL1A2 (38-kb size, located on the long arm of chromosome 7) genes that encode the two pro-α1(I) and one pro-α2(I) chains of the type I procollagen trimer, respectively. These genes contain more than 50 exons to generate about 1,450 amino acids of each chain. The formation of the essential triple helical structure of procollagen I from these three pro-α(I) chains depends on the presence of glycine in every third position in the 1,014-residue triple helical domain and is stabilized by the presence of hydroxyproline. The triple helix is propagated from the carboxyl-terminal end toward the amino-terminal end of the molecule. The mature molecule is then secreted from the cell into the extracellular matrix, where the amino-terminal and carboxyl-terminal propeptides are removed enzymatically and type I collagen fibrillogenesis occurs by self-assembly.[2,15-18]

More than 150 mutations of the COL1A1 and COL1A2 genes, including single base-pair changes, deletions, insertions, premature stop codons, and splicing mutations, have been described, causing forms of OI ranging in phenotype from mild to lethal. The most frequent mutation types are single base-pair substitutions in either of the two alleles that alter a codon for glycine in the triple helical domain of the chain.

The molecular basis of Sillence type I OI remains poorly understood. Cells from affected individuals largely demonstrate a quantitative defect of type I collagen; they synthesize and secrete about half the normal amount of type I procollagen. This is due to decreased synthesis of pro-α1(I) chains; in general, the pro-α2(I) chain is normal. The mutation often occurs in one allele, resulting in about half the normal amount of the molecule, as type I procollagen must contain two pro-α1(I) chains.

The vast majority of infants with type II OI appear to be heterozygous for mutations that result in substitutions for glycine residues within the triple helical domain of either the pro-α1(I) or the pro-α2(I) chain. In some instances, exon-skipping mutations in either gene can result in this phenotype. Type III and type IV phenotypes can also result from heterozygosity for point mutations of glycine residues within the triple helical domains of either chain of type I procollagen or from exon-skipping mutations.[2,15-18]

There are several basic concepts concerning the nature of mutations and their phenotypic consequences. Quantitative mutations that decrease expression and synthesis of normal type I procollagen molecules result in milder phenotypes, such as type I OI. Qualitative mutations that lead to structural aberrations and abnormal type I procollagen result in more severe phenotypes, such as types II and III. The severity of the phenotype reflects the location of the mutation within the chain, the nature of the mutation, and the chain in which the mutation occurs. In general, with point mutations, the phenotype becomes milder as the mutation is shifted toward the amino-terminal end of the chain, because the essential triple helical structure is formed from the carboxyl-terminal end toward the amino-terminal end in a zipperlike helical-coiling manner. With glycine substitution mutations, amino acid replacements with bulkier side chains, such as arginine, result in more severe phenotypes than those with smaller side chains, such as serine and cysteine. Mutations in the COL1A2 gene have milder consequences than similar mutations in the COL1A1 gene, as the type I procollagen molecule has two pro-α1(I) chains and one pro-α2(I) chain.[2,15-18]

The expression of these mutations into the observed phenotypic patterns is poorly understood. On the molecular level, these mutations can decrease the rate of synthesis, decrease the thermal stability of the triple helical molecules, delay the rate of folding of the precursor procollagen molecule, increase the level of aberrant post-translation modification of procollagen chains, and impair the rate of export of molecules from cell to matrix. Mutated chains are more slowly incorporated into fibrils than normal collagen molecules; demonstrate an abnormal configuration, with more branching, shortening, or thickening; and impair mineralization by providing a mutated structural template for incorporation of hydroxyapatite crystals. The end result of these molecular changes eventually translates into the microscopic and gross pathologic features characteristic of OI.[2,15-19]

The identification of a vast array of genetic mutations associated with OI is commensurate with the observed phenotypic heterogeneity of this disease. This supports the concept that OI represents a continuum of mutational events translating into a continuum of phenotypic involvement from perinatal lethal forms to moderate deforming forms to mild, nondeforming forms. Included in this continuum would be type VII Ehlers-Danlos syndrome and some variants of osteoporosis. In type VIIA and type VIIB

Ehlers-Danlos syndrome, the molecular abnormality is impaired cleavage of the N-terminal propeptides from procollagen secondary to mutations in the COL1A1 and COL1A2 genes. Phenotypically, this results in joint hypermobility, skin changes, and other signs of connective tissue involvement. Thus, any classification system of OI must impose arbitrary boundaries within this continuum. However, for purposes of facilitating communication, predicting natural history, and planning management strategies, it seems reasonable to continue classifying into clinical subtypes, such as the Sillence classification or the congenita-tarda schemes. These groupings represent a series of syndromes related to classes of molecular defects, each with a reasonably well-defined phenotypic pattern.

Management

Systemic Therapy

Several systemic treatments for OI have been attempted, but all have been ineffective or inconclusive or are still experimental. Two features of OI make evaluation of the efficacy of therapeutic interventions difficult. First, the large genetic and biochemical heterogeneity in OI results in trials that combine patients with different mutations. Thus, a treatment that may benefit individuals with specific mutations and biochemical defects may be ineffective for other patients with different mutations and biochemical defects. Second, the frequency of fractures within the same patient can differ dramatically from one time period to another. Thus, studies that use fracture frequency or linear growth to evaluate efficacy without well-matched controls may show improvement unrelated to drug effect.[2]

Calcitonin has been used because of its osteoclastic inhibitory effects and resultant increase in bone density in osteoporosis. Results in patients with OI have been mixed, with some studies finding decreased fracture frequency and increased bone density, and other studies finding no effect and high side-effect profiles. Similarly, sodium fluoride, calcium, anabolic steroids, growth hormone, magnesium oxide, vitamin C, and vitamin D have been tried in OI patients with mixed results and failure to demonstrate definite treatment value. The efficacy of bisphosphonates in increasing bone mineral content and density while reducing bone resorption in patients with OI has not yet been established.[1,2]

Although still strictly theoretical, conceivably the most dramatic and efficacious form of treatment for OI and related disorders would be gene therapy. In Sillence type I OI, this could involve stimulation of type I collagen synthesis. In the more severe types, this could involve replacement of the defective gene. In one series of experiments, researchers developed a modified oligonucleotide that specifically inhibited expression of a mutated gene for the pro-α1(I) chain of type I procollagen by 50% to 80% in cell culture studies. There are considerable technical barriers involved in an oligonucleotide design and delivery system in vivo; however, the potential optimal effect may be to convert a severely debilitating phenotype to a milder form of the disease through inhibition of expression.[2,15] In another series of experiments, researchers developed a transgenic mouse line that expressed an antisense RNA for the pro-α1(I) chain. When bred to mice that expressed a phenotype of severe brittle bones, offspring that expressed both genes had a marked decrease in lethality and an increase in the incidence of brittle bones, presumably because they had a rescue phenotype.[2,15]

Orthopaedic Management

The overall goals of treatment of OI are to maximize function, minimize disability, achieve relative independence in activities of daily living, attain the greatest possible degree of mobility, allow social integration, and maintain overall health. This requires a team approach from the health-care providers, including the pediatrician, orthopaedic surgeon, geneticist, neurologist, neurosurgeon, dentist, ophthalmologist, physical therapist, social worker, and nurse-clinician. Care must be individualized, depending primarily on the severity of the disease and the age of the patient. Sillence type I OI, in its milder forms, may have only a minimal impact on the patient, and the role of the orthopaedic surgeon is limited to conventional fracture care. Early death often occurs in type II OI before any orthopaedic intervention is indicated. Type III and type IV present the greatest management challenges for the orthopaedist in terms of fracture prevention, fracture management, limitation of deformity, and optimization of function.[20-22]

The management of OI begins with early detection in utero for pregnancies at risk to guide in family planning and obstetric management. In the neonate with deforming OI (type III and some type IV), immediate life-threatening problems of respiratory insufficiency and intracranial hemorrhage are managed by the neonatologist. In utero fractures have usually healed, and recent fractures often do not require special treatment other than splinting. The parents should be educated about handling of the infant and about the natural history of the disease. Lay organizations, such as the OI Foundation, are helpful with parental education.

In infancy and childhood, physical therapists can be instrumental

in optimizing normal development patterns as the infant develops trunk control and functional limb use. The orthopaedist is involved in helping to obtain the greatest degree of mobility possible and in the treatment of fractures, which can be frequent. When fractures occur, one should use as little immobilization as possible to prevent overall deconditioning, worsening the extent of osteopenia, and increasing the risk of further fracture. In severe OI, the multiplicity of fractures, the underlying osteoporotic bone, and the abnormal mechanical stresses on malaligned bones can lead to further fractures and deformity, interfering with the ability to stand and walk. External support from orthoses or splints may be necessary to optimize function. Deformity that is impairing function can be addressed surgically by multiple osteotomies and intramedullary fixation.

Fracture rates almost always decrease dramatically after puberty, but increases have been documented in women after menopause and in men after age 60. Pregnancy in women with OI requires special obstetric management due to increased fracture risk, pelvic dysplasia, and metabolic abnormalities.

Nonoperative treatment is the mainstay of orthopaedic management of OI. Depending on disease severity, a comprehensive and progressive program of mobilization and bracing is pursued for patients with ambulatory potential, and a program of appropriate seating and wheelchair locomotion is pursued for nonambulatory patients. The goal is to emphasize ultimate independent function and to maximize social integration.[20-22] Lightweight bracing can be helpful for external structural support to promote stance and locomotion and for the prevention and treatment of fractures. Pneumatic trouser splints and vacuum pants have been introduced to support fragile bones, improve mobility, and maintain alignment after fracture or closed osteoclasis.[23]

Closed treatment methods are the mainstay of fracture management. Fractures generally heal, often with exuberant callus but with the same abnormal bone quality. The difficulty in fracture management lies in the prevention of deformity and the vicious circle associated with immobilization—deconditioning, osteoporosis, and increased fracture risk. Lightweight splints and braces are most often used, with the emphasis on early mobilization.

Operative intervention is indicated for recurrent fractures or deformity that impairs function. The optimal age for surgical intervention is controversial; some recommend early intervention with elongating rods, but traditional management involves accepting deformity from closed treatment until the patient is about 5 years old and then proceeding to corrective osteotomies.

Various techniques for deformity correction have been espoused, including closed osteoclasis with traction followed by pneumatic splints (Morel technique), closed osteoclasis with percutaneous intramedullary nailing,[24] multiple corrective osteotomies with intramedullary nailing (Sofield-Millar technique)[25,26] (Fig. 6), and osteotomies with elongating intramedullary (Bailey-Dubow) rods.[27,28]

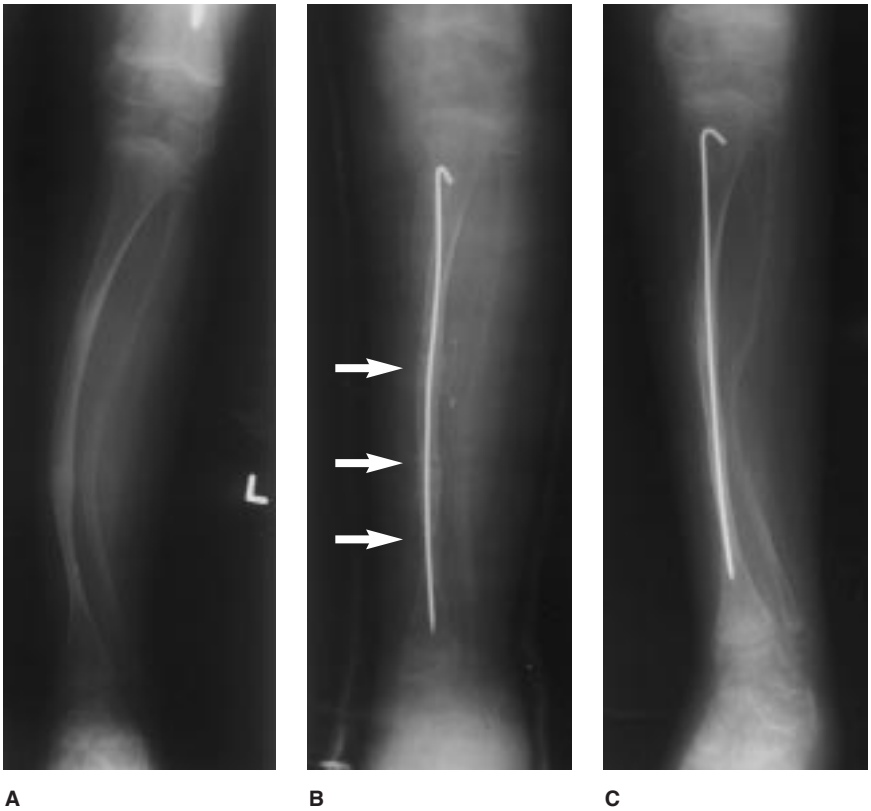

Fig. 6 Leg deformity in a patient with type III OI. **A,** Preoperative AP radiograph obtained at age 6 years demonstrates deformity. **B,** Postoperative film with leg in cast shows multiple osteotomies (arrows) with intramedullary fixation. **C,** Film obtained after healing of osteotomies.

Management must be highly individualized, taking into account personal experience, the severity of the patient's deformity, the diameter of the long bones, and the advantages and complications of each technique. Elongating rods have a decreased replacement rate when compared with nonelongating rods; however, they are weaker; traverse the physis; are technically more demanding, as they require a larger medullary canal and central placement; and are associated with complications related to disassembly and nonelongation.[27,28]

General principles in the surgical management of OI include avoiding surgery in patients under age 2 years, avoiding plate-and-screw fixation in favor of intramedullary fixation, and use of gentle technique for muscle preservation and minimization of soft-tissue bleeding. Bone-holding clamps should be avoided, as they can crush fragile bone. Radiographic control is essential, as the deformities are often three-dimensionally complex, necessitating different views.

When multiple osteotomies are performed, the individual fragments should be as long and straight as possible. Placement of osteotomies in diaphyseal regions enhances stability with intramedullary rods. Some bone shortening may be necessary when there are severe deformities, as the taut soft-tissue structures on the concave side can be stretched excessively when deformity is corrected. Reaming may occasionally be necessary for rod placement. Violation of the growth plate should be avoided when possible. Immobilization with casting or braces until bone union is almost always necessary.

The anesthesiologist should be aware of the increased risk of malignant hyperthermia in patients with OI. Anesthetic principles include avoiding the use of atropine, careful metabolic monitoring, not insulating the patient with large numbers of drapes, and aborting the operation at the earliest signs of hyperthermia.[8] Patients with OI may have platelet and coagulation abnormalities, and perivascular fragility due to collagen abnormalities may predispose to bleeding. Blood loss and insensible losses due to hypermetabolism should be carefully monitored.

Spinal deformity in patients with OI is difficult to manage. Truncal shortening of thoracolumbar spinal segments can occur secondary to collapse of osteopenic vertebrae. If the patient is symptomatic, a soft spinal orthosis is helpful. Scoliotic and kyphoscoliotic curves often progress rapidly. The soft, deformed rib cage and truncal shortening combine to render bracing relatively ineffective, but it can be helpful in mild forms of OI and as a sitting aid for the nonambulator.

In milder forms of OI, bracing can be utilized for curves of 20 to 40 degrees or kyphosis greater than 40 degrees. Spinal fusion has been recommended for scoliotic curves greater than 45 degrees to halt progression (Fig. 7). For patients with more severe involvement, bracing is ineffective and can produce thoracic cage deformity; fusion is recommended for curves over 35 degrees, as these curves are most often progressive and potentially severe. There is a high incidence of complications from spinal fusion in OI, because internal fixation is limited by poor bone quality, autogenous iliac-crest bone graft is limited, and patients have a propensity to bleeding.[3,29]

Summary

Osteogenesis imperfecta is a remarkable disorder. Recent clinical, genetic, and molecular investiga-

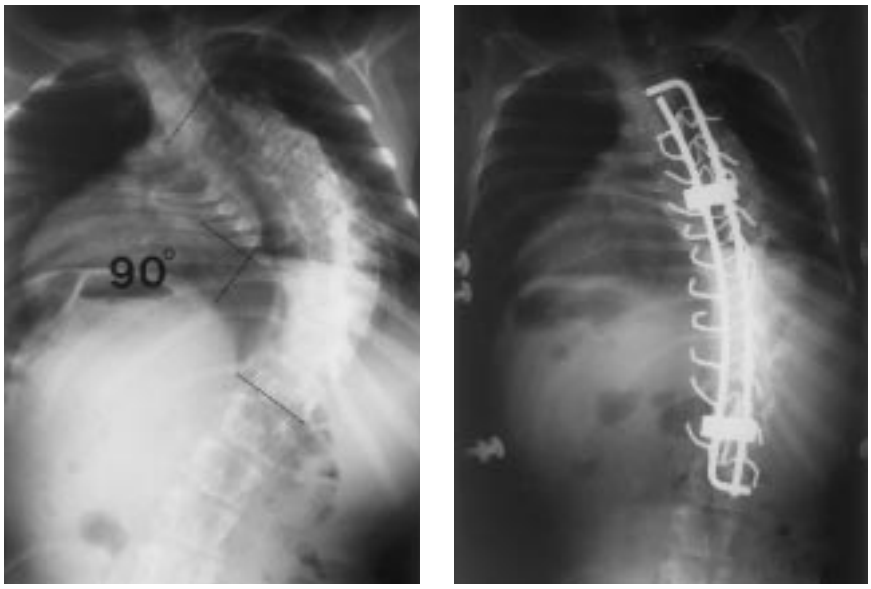

Fig. 7 Rapidly progressive spinal deformity in a 12-year-old child with type III OI. **A,** Preoperative AP radiograph shows a 90-degree right thoracic curve with severe rib deformities at the curve concavity. **B,** AP film obtained after spinal fusion with Luque instrumentation.

tions have characterized its heterogeneous phenotypic and genotypic features. In addition, insight has been gained from investigations into the altered collagen chemistry and its effect on the structure and function of bone.

Ongoing research holds great promise for the treatment of OI. The potential for gene therapy to increase the synthesis of type I collagen in mild variants and to correct mutations in severe variants lies ahead, but there are a great number of technical difficulties to overcome. Further understanding of how genotypic mutations lead to abnormal molecular structure and then abnormal bone structure is essential.

As long as the potential for gene therapy remains distant, well-designed controlled trials with systemic treatment modalities are needed. Ideally, these would direct specific interventions to patients with particular biochemical abnormalities, recognizing the underlying heterogeneity of the disorder. The development of registries including both phenotype and genotype would catalog this new classification of patients and would facilitate defect-specific trials. Development of comprehensive treatment teams to address the multiple health-care needs of OI patients will ultimately help them achieve goals of relative independence and social integration.

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