1b. Clinical Conditions

Introduction

CLINICAL COMMENTARY 2-1
Osteogenesis Imperfecta, an Inherited Collagen Disorder

As its name implies, osteogenesis imperfecta is a disease caused by defects in the formation of bone. This disorder, sometimes known as brittle bone disease, affects approximately 1 in 15,000 to 1 in 25,000 births in all ethnic groups.

Approximately 90% of osteogenesis imperfecta cases are caused by defects in type I collagen, a major component of bone that provides much of its structural stability. The function of collagen in bone is analogous to that of the steel bars incorporated in reinforced concrete.

When type I collagen is improperly formed, the bone loses much of its strength and fractures easily. Patients with osteogenesis imperfecta can suffer hundreds of bone fractures (Fig. 2-14), or they might experience only a few, making this disease highly variable in its expression (the reasons for this variability are discussed in Chapter 4). In addition to bone fractures, patients can have short stature, hearing loss, abnormal tooth development (dentinogenesis imperfecta), bluish sclerae, and various bone deformities, including scoliosis. Osteogenesis imperfecta was traditionally classified into four major types, all of which are caused by mutations in either of the two genes that encode type I collagen. Several additional types, caused by mutations in other genes, have subsequently been added (Table 2-3). There is currently no cure for this disease, and management consists primarily of the repair of fractures and, in some cases, the use of external or internal bone support (e.g., surgically implanted rods). Additional therapies include the administration of bisphosphonates to decrease bone resorption and human growth hormone to facilitate growth. Physical rehabilitation also plays an important role in clinical management.

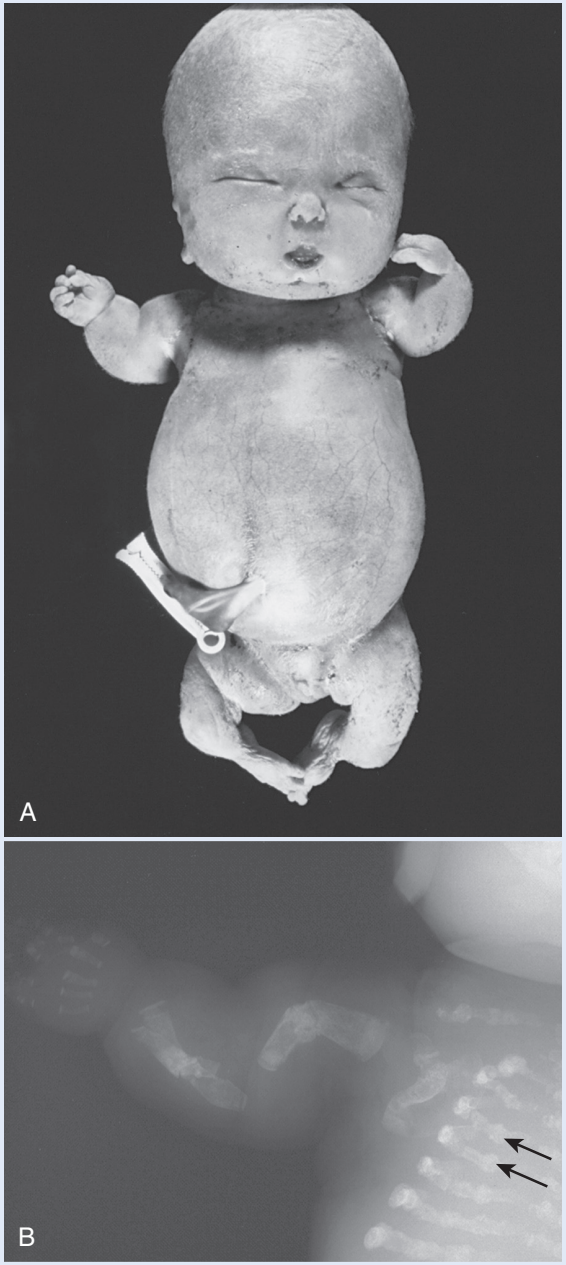

FIG 2-14 A, A stillborn infant with type II osteogenesis imperfecta (the perinatal lethal form). The infant had a type I procollagen mutation and short, slightly twisted limbs. **B,** Radiograph of an infant with type II osteogenesis imperfecta. Note calluses from rib fractures, which are observable as "beads" on the ribs *(arrows)*.

TABLE 2-3 Subtypes of Osteogenesis Imperfecta

TYPE	DISEASE FEATURES
I	Mild bone fragility, blue sclerae, hearing loss in 60% of patients, normal or near-normal stature, few bone deformities, dentinogenesis imperfecta in some cases
II	Most severe form, with extreme bone fragility, long bone deformities, compressed femurs, gray-blue sclerae; lethal in the prenatal or perinatal periods (most die of respiratory failure during the first week of life, and survival beyond one year is highly unusual)
III	Severe bone fragility, very short stature, variably blue sclerae, progressive bone deformities, hearing loss in 80% of patients; dentinogenesis imperfecta is common
IV	Short stature, normal-to-gray sclerae, mild to moderate bone deformity, hearing loss in some patients, dentinogenesis imperfecta is common; bone fragility is variable
V	Similar to type IV but also includes calcification of interosseous membrane of forearm, radial head dislocation, and hyperplastic callus formation
VI	Similar to type IV but not caused by type I collagen mutations; calcification in interosseous membranes is not seen; no dentinogenesis imperfecta
VII	White sclerae, early lower limb deformities, shortening of all limbs, congenital fractures, osteopenia
VIII	Severe, often lethal phenotype similar to type II but not caused by type I collagen mutations; severe osteoporosis, shortened long bones, white sclerae

Types I-IV are caused by mutations in the two genes that encode type I collagen protein; types V-VIII have been identified on the basis of distinct bone histology and are caused by mutations in genes involved in posttranslational processing of the gene product. Types VII and VIII have an autosomal recessive mode of inheritance, and several additional rare autosomal recessive forms of osteogenesis imperfecta have been identified. There is substantial phenotypic overlap among many of these categories of osteogenesis imperfecta.

Type I collagen is a trimeric protein (i.e., having three subunits) with a triple helix structure. It is formed from a precursor protein, type 1 procollagen. Two of the three subunits of type 1 procollagen, labeled pro-α1(I) chains, are encoded by an 18-kb (kb = 1000 base pairs) gene on chromosome 17, and the third subunit, the pro-α2(I) chain, is encoded by a 38-kb gene on chromosome 7. Each of these genes contains more than 50 exons. After transcription and splicing, the mature mRNA formed from each gene is only 5 to 7 kb long. The mature mRNAs proceed to the cytoplasm, where they are translated into polypeptide chains by the ribosomal machinery of the cell.

At this point, the polypeptide chains undergo a series of posttranslational modifications. Many of the proline and lysine residues* are hydroxylated (i.e., hydroxyl groups are added) to form hydroxyproline and hydroxylysine, respectively. (Several rare forms of osteogenesis imperfect, including type VII, are caused by mutations in genes involved in the hydroxylation process.) The three polypeptides, two pro-α1(I) chains, and one pro-α2(I) chain, begin to associate with one another at their COOH termini. This association is stabilized by sulfide bonds that form between the chains near the COOH termini. The triple helix then forms, in zipper-like fashion, beginning at the COOH terminus and proceeding toward the NH_2 terminus. Some of the hydroxylysines are glycosylated (i.e., sugars are added), a modification that commonly occurs in the rough endoplasmic reticulum (see Fig. 2-1). The hydroxyl groups in the hydroxyprolines help to connect the three chains by forming hydrogen bonds, which stabilize the triple helix. Critical to proper folding of the helix is the presence of a glycine in every third position of each polypeptide.

Once the protein has folded into a triple helix, it moves from the endoplasmic reticulum to the Golgi apparatus (see Fig. 2-1) and is secreted from the cell. Yet another modification then takes place: the procollagen is cleaved by proteases near both the NH_2 and the COOH termini of the triple helix, removing some amino acids at each end. These amino acids performed essential functions earlier in the life of the protein (e.g., helping to form the triple helix structure, helping to thread the protein through the endoplasmic reticulum) but are no longer needed. This cleavage results in the mature protein, type I collagen. The collagen then assembles itself into fibrils, which react with adjacent molecules outside the cell to form the covalent cross-links that impart tensile strength to the fibrils.

The path from the DNA sequence to the mature collagen protein involves many steps (Fig. 2-15). The complexity of this path provides many opportunities for mistakes (in replication, transcription, translation, or posttranslational modification) that can cause disease. Of the more than 1500 type I collagen mutations now known to cause osteogenesis imperfecta, the most common type produces a replacement of glycine with another amino acid. Because only glycine is small enough to be accommodated in the center of the triple helix structure, substitution of a different amino acid causes instability of the structure and thus poorly formed fibrils. This type of mutation is often seen in severe forms of osteogenesis imperfecta. Other mutations can cause excess posttranslational modification of the polypeptide chains, again producing abnormal fibrils. Other examples of disease-causing mutations are provided in the suggested readings at the end of this chapter.

*A residue is an amino acid that has been incorporated into a polypeptide chain.

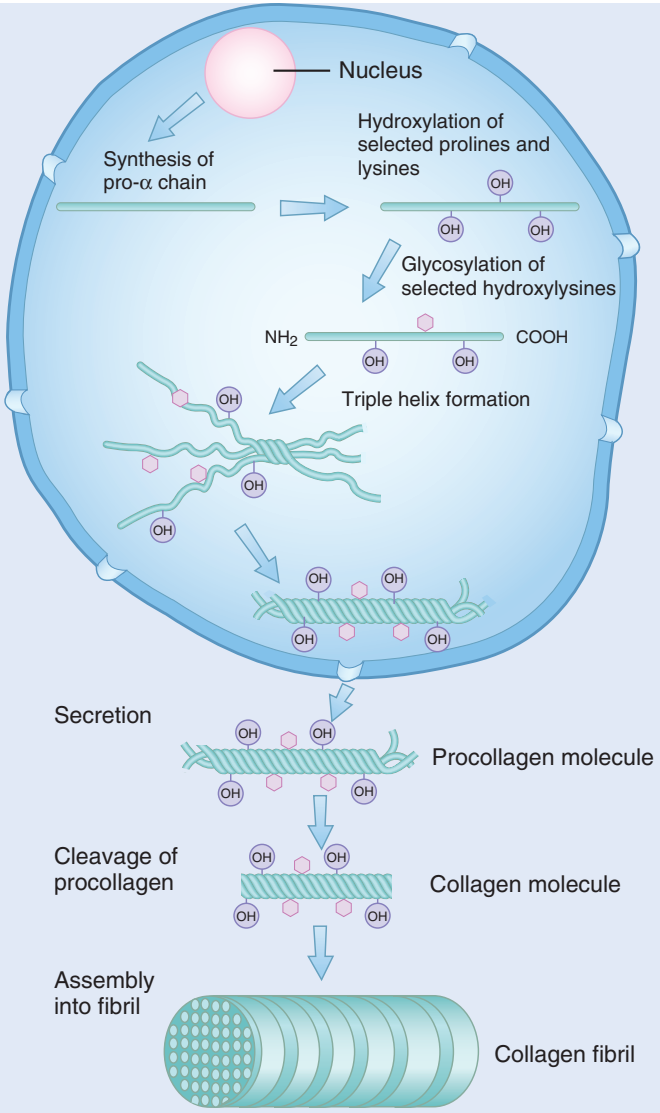

FIG 2-15 The process of collagen fibril formation. After the pro-α polypeptide chain is formed, a series of posttranslational modifications takes place, including hydroxylation and glycosylation. Three polypeptide chains assemble into a triple helix, which is secreted outside the cell. Portions of each end of the procollagen molecule are cleaved, resulting in the mature collagen molecule. These molecules then assemble into collagen fibrils.