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Osteogenesis imperfecta

Francis H. Glorieux*

Professor of Surgery, Pediatrics and Human Genetics

Genetics Unit, Shriners Hospital for Children, 1529 Cedar Avenue, McGill University, Montréal, Québec, Canada H3G 1A6

Osteogenesis Imperfecta is a heritable disorder characterized by bone fragility and low bone mass, with a wide spectrum of clinical expression. This review gives an update on its classification, the recent developments in the understanding of its pathophysiological mechanisms, and the current status of bisphosphonate therapy. Other therapeutic approaches and future directions of research are briefly discussed.

Key words: osteoporosis; bisphosphonates; type I collagen; osteogenesis imperfecta.

Osteogenesis imperfecta (OI), a heritable disorder of bone formation, is characterized by bone fragility and low bone mass.[1] Its overall incidence is approximately one in 10 000 births. Bone fragility has led to the trivial name of 'brittle bone disease'. The heritable nature of the disorder distinguishes it from idiopathic juvenile osteoporosis, although clinical osteoporosis is also a consequence of OI. Patients with OI do not have perturbations in mineral homeostasis and vitamin D metabolism as a consequence of their disease.

Extraskeletal clinical features of OI include blue sclera, dentinogenesis imperfecta, skin hyperlaxity and joint hypermobility. Such features suggest an association with abnormalities involving type I collagen, although such a relationship is not absolute. In addition, OI patients may present with Wormian bones in the sutures of the skull, decreased height and skeletal deformities.

The broad clinical spectrum of the disease was quickly recognized and comprehensive classification systems were proposed. The one in common use today was presented by Sillence et al and subdivides patients into four types based on disease severity and progression.[2] However, it is appreciated that, in reality, the disorder represents a continuum of severity and that patients do not always fall conveniently into one clinical category. Bone histology has also revealed that individuals with a similar

* Tel.: +1 514 842 5964; Fax: +1 514 842 5581.
E-mail address: glorieux@shriners.mcgill.ca

clinical presentation may exhibit vastly different changes in bone tissue organization. This has led to further subdivisions of the disorder, with seven subtypes having been defined.

There has been a tendency in the past decade to define OI as a type I collagenopathy.[3,4] This would imply that most, if not all, OI must arise from a mutation in either one of the two genes encoding type I collagen, *COL1A1* and *COL1A2*. However, there are a considerable number of individuals in whom such mutations are absent, and a mutation in a different gene is likely to be the causative event.[5–7] Therefore, the definition of OI should remain clinical. It is possible that in the future, genetic diversity may result in a new classification of the disease.

CLASSIFICATION

The classification system of Sillence et al divides OI into four severity-based types, with Type IV representing the most clinically diverse group.[2] It is from this heterogeneous group that Types V, VI and VII have been identified on the basis of distinct clinical and histological features.[8–10] The most clinically relevant characteristic of all types of OI is bone fragility, the severity of which increases in the order Type I $<$ Types IV, V, VI, VII $<$ Type III $<$ Type II. Heredity follows an autosomal-dominant pattern in Types I through V, and is autosomal recessive in Types VI and VII. Mutations affecting collagen type I are usually present in Types I through IV, but are absent in Types V, VI and VII (Table 1).

Type I OI, the most common and mildest form of the disease, is non-deforming and results in patients attaining close to a normal height. However, vertebral fractures are common and can lead to mild scoliosis. Patients typically have blue sclera and (infrequently) dentinogenesis imperfecta. Fractures are rarely observed at birth, but begin with ambulation and subsequent falls during juvenile development, then commonly decrease following puberty.

Type II OI is the most severe form, resulting in death in the perinatal period. These individuals exhibit multiple intra-uterine rib and long bone fractures, and severe skeletal deformities, which eventually result in respiratory failure. Bone histology reveals a marked decrease in both cortical bone thickness and the amount of trabecular bone.

Type III OI is the most severe form of the disease, compatible with survival past the perinatal period. It is characterized by severe progressive skeletal deformities often starting from birth. Fractures may be present in utero and are very common during the growing period. The incidence of fractures remains high even in adult life. Individuals have severely short stature and, because of their deformities and bone fragility, are frequently confined to a wheelchair for life. Scoliosis can lead to respiratory problems, which have been identified as a leading cause of death in this patient group.[11,12] Dentinogenesis imperfecta is often present.

Type IV OI is the most clinically diverse group. The phenotype can vary from severe to mild, with the more severely affected patients presenting with fractures at birth, suffering moderate skeletal deformities and attaining a relatively short stature.

Type V OI is moderately deforming, and patients suffer from moderate to severe bone fragility.[8] Blue sclera and dentinogenesis imperfecta are not present. There are three distinctive features: the frequent development of hypertrophic calluses at fracture sites; the calcification of the interosseous membranes between the bones of the forearm; and the presence of a radio-opaque metaphyseal band immediately adjacent to the growth plates on x ray. Upon histological examination, the bone organization has an irregular mesh-like appearance, clearly distinct from the normal lamellar pattern.