Osteogenesis imperfecta (OI) is the most common inherited disease that causes bone fragility, occurring with a frequency of 1 in 5,000 to 1 in 10,000 births (1). The majority of OI patients (85%-90%) have mutations in the genes encoding type I collagen; however, over the last ten to fifteen years, defects in genes encoding proteins involved in collagen processing, folding, and stability as well as in osteoblast differentiation or function have also been described (2). Patients with milder forms of OI generally have normal collagen, albeit in reduced quantities, while patients with more severe forms generally have abnormal collagen, collagen metabolism defects, or osteoblast-related pathway abnormalities.

The degree of bone fragility ranges from apparently mild, with occasional fractures and minimal effects on bone shape or length, to severe, progressively deforming disease with many fractures, which can exceed 200 fractures during childhood. Severe bone fragility can be lethal in utero (multiple rib fractures can result in failure of lung development, and the abnormal skeleton can fail to protect internal organs, including the brain) or later in life (due to the effects of scoliosis or the invagination of the odontoid peg into the brain stem). Patients with such conditions undergo multiple corrective surgical procedures, with most individuals experiencing bone pain, reduced mobility, and below-average stature; severely affected individuals are very short. Ligamentous laxity can also be a prominent feature, exacerbating pain and mobility problems. Dentinogenesis imperfecta can result in teeth chipping and cracking, accelerated dental decay, and tooth loss. Patients with severe OI can also experience hernias, heart valve prolapse, and mixed conductive and sensorineural hearing loss, which all increase in frequency with age.

**Current therapies**

Management of OI is multidisciplinary. The standard of care includes pain management, therapy input for muscle strength and range of movement, aids to daily living and mobility, psychologic and social support, and regular monitoring of dentition and hearing. Surgical input to straighten deformed bones, correct scoliosis, and remove the odontoid peg requires specialist orthopedic and neurosurgical team involvement. Some profoundly deaf OI patients may benefit from cochlear implants, and most individuals with OI require special dental input.

The use of bisphosphonates in children with OI has been shown to significantly increase bone mineral density and reduce fractures (3, 4). Anecdotal reports often speak of children having “increased energy” and less pain after bisphosphonate treatment. The introduction of bisphosphonate therapy in multiple treatment centers during the 1990s led to a step-change in outcomes for children, although the effect on life-limiting complications such as scoliosis is unclear.

In contrast, the benefits of bisphosphonates for adults with OI are less well proven (5). Moreover, long-term use of antiresorptive treatment may be associated with an increased risk of atypical femoral fractures in patients with OI and osteoporosis (6). Therefore, it is important to further investigate anabolic treatment options for adults with OI.

**Research advances**

In this issue of the JCI, a report by Orwoll and colleagues (7) suggests a positive effect on bone mass after teriparatide treatment in individuals with OI, particularly those at the mild end of the disease spectrum. A previous report of thirteen postmenopausal women with mild OI also showed a positive bone mineral density and bone biochemical marker response after teriparatide treatment (8). Based on the positive results of these studies, the effects of anabolic therapy for increasing bone mass and reducing fracture risk deserve further exploration. Future studies should evaluate treatment responses for longer periods as well as the effects of teriparatide treatment alone and in combination with antiresorptive therapies.

While the results of Orwoll and colleagues (7) are promising for patients with milder disease, they are perhaps disappointing for patients with more severe disease, who are more likely to have fractures and progressive problems in adulthood. The current lack of proven treatment options for patients with severe OI highlights the importance of nonpharmacological approaches for disease management and the need for multidisciplinary team resources for adults, which are often less comprehensive than the resources in pediatrics.
intake and vitamin D sufficiency are simple adjuncts to any other therapeutic intervention. Aids to mobility are not required in this instance, but regular monitoring of hearing and dentition is important; 50% of adults with OI have substantial hearing loss by 50 years of age. Unfortunately, having OI does not preclude patients from age-associated bone loss, and menopausal bone loss still occurs in women with OI; therefore, regular review in a specialist bone clinic is an effective way to ensure appropriate monitoring for potential problems. Because adults with OI are often weak, the patient in this instance might benefit from physiotherapy to strengthen muscles, especially in the core or hip girdle. For those with reduced mobility, occupational therapy input allows for improvements in activities of daily living, often through simple adjustments to home and work environments. Adults as well as children need access to specialized services that can meet their multiple needs in a coordinated and holistic manner. Until we have proven therapies that can substantially alter and improve bone material quality, bone fragility, deformity, and pain, patients with severe OI will likely need ongoing support to limit damage and ensure a good quality of life.

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