A 42-year-old premenopausal woman with osteogenesis imperfecta presents to the metabolic bone clinic. She has a daughter with osteogenesis imperfecta who is seen regularly in a specialist pediatric clinic, but the patient herself hasn’t had a clinical consultation in years. She has pain and stiffness in her back and is worried for her future bone health. The patient asks, “Am I going to fall apart?” She had numerous fractures in childhood, including fractures of her femur and wrist; fractured her ankles several times in her late teens; and had occasional fractures in adulthood. Her last fracture was a comminuted fracture of her humerus three years ago, when she stumbled and fell forward onto her hands and knees. The woman is hyperextensible and thinks her ankles feel weak. Her bone mineral density T scores are −2.6 at the lumbar spine and −1.9 at the total hip, and spine imaging shows several vertebral endplate deformities, but overall preservation of vertebral height. What are the available pharmacological and nonpharmacological strategies to preserve her skeletal health and function?

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 specialist 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.

Recommendations

In terms of our patient described above, lifestyle measures may help to preserve her bone health. Ensuring good dairy product...
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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