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Osteogenesis imperfecta-a current overview

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ABSTRACT

A genetically diverse condition called osteogenesis imperfecta (OI) is characterized by low bone mass and fragility. Over the past few decades, OI has evolved from an illness lacking a known etiology to one with a well-defined and well-mapped genetic background. Pathogenic mutations in COL1A1/COL1A2 with autosomal-dominant inheritance are linked to most cases of OI. The pathophysiology of OI is now well understood thanks to recent gene discoveries, which has opened up new opportunities for treatment development. The main characteristics of OI patient include short stature, bone abnormalities, and repeated fractures. Joint hypermobility, dentinogenesis imperfecta, blue sclera, hearing loss, and, less frequently, muscle weakness, pulmonary, and cardiovascular problems are examples of extraskeletal symptoms. In addition to pharmaceutical therapy, OI requires interdisciplinary care from orthopedic management, rehabilitation, nutrition, dentistry, and other subspecialties. Although the current pharmacologic therapy for OI does not address the matrix defect that is the main cause of bone fragility, it may enhance bone mass and morphology. To develop treatments that will target the genetic flaw and mechanism causing OI, research is still being done.

Keywords: Bone diseases, collagen type 1, genetic background, osteogenesis imperfecta

INTRODUCTION

Osteogenesis imperfecta (OI), also called brittle bone disease, is a genetic disorder affecting the extracellular matrix.[1] It is a systemic connective tissue condition characterized by reduced bone density and fragility, leading to significant morbidity from pain, limited mobility, skeletal deformities, and growth impairment. The weakened bones result in low-trauma fractures or fractures in unusual locations, such as the olecranon and vertebral compression fractures. OI also presents with various extraskeletal symptoms including dental irregularities, blue-gray sclera, hearing impairment, joint hypermobility, and, more rarely, muscle weakness, cardiovascular issues, and pulmonary complications.[2-4] Recent technological advancements have made it possible to diagnose OI as early as the first to early second trimester. In the past, it was only possible to suspect OI in the second trimester using ultrasound, and confirming the diagnosis necessitated invasive genetic testing. Detecting OI early, particularly in severe or lethal cases, could offer ample time to empower the parents in making decisions regarding termination of pregnancy, mode of delivery, resuscitation at birth, treatment options, and seeking genetic counseling for future pregnancies.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The incidence of OI is approximately 1 in 10,000.[4] OI is a skeletal dysplasia with genetic diversity and a higher mortality rate compared to the general population. Folkestad et al.[5] discovered that individuals with OI have an increased risk of death due to respiratory and gastrointestinal diseases as well as trauma. In most instances, OI is inherited in an autosomal-dominant manner, although autosomal-recessive and X-chromosome-linked variations of the disease have also been documented. The majority of OI cases (about 85-90%) are linked to dominantly inherited mutations in COL1A1 or COL1A2, which are responsible for encoding type I collagen. To date, over 1500 dominant mutations in the COL1A1 and COL1A2 genes have been identified.[6,7] Pathogenic variants in noncollagenous genes are responsible for the remaining cases, which encode proteins involved in collagen biosynthesis. These variants can also be related to transcription factors and signaling molecules that are involved in bone cell differentiation and mineralization. The inheritance associated with these cases is most commonly autosomal-recessive, but can also be dominant or X-linked.[2-4]

CLASSIFICATION

The severity of OI can vary from a subtle increase in fracture frequency to perinatal death. According to the revised nosology and classification of genetic skeletal disorders, there are 5 clinical forms of OI: OI type I, known as 'nondeforming

with blue sclera'; OI type II, referred to as 'perinatally lethal OI'; OI type III, categorized as 'progressively deforming OI'; OI type IV, labeled as 'moderate severe OI' (**Figure**); and OI type V, which is distinguished by moderate-to-severe bone fragility and a calcified interosseous membrane. OI type V follows an autosomal-dominant pattern, and a hyperplastic callus may form after fractures or surgical interventions.[8-10] There are also other phenotypes, such as Bruck syndrome, a severe OI phenotype that is linked to joint contractures.[11]

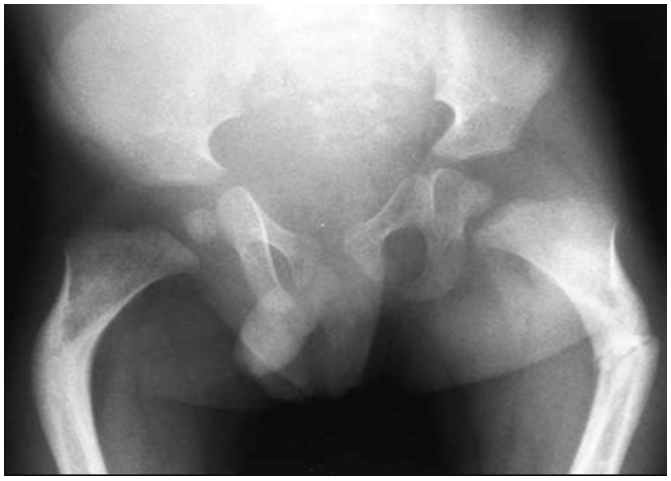

Figure. Osteogenesis imperfecta type IV. Radiograph showing subtrochanteric deformities and a pathological fracture of the femur

DIAGNOSIS

The diagnosis of OI is based on radiographic abnormalities, bone biochemistry, lumbar spine bone mineral density (BMD), history, and clinical examination.[12] It's critical to rule out metabolic causes of osteoporosis. The most significant clinical characteristic, shared by all OI types, is bone fragility, while additional extra-skeletal characteristics may also exist. It is possible to make a diagnosis during pregnancy, at birth, in childhood, or in adulthood.

For the prenatal diagnosis of OI, diagnostic modalities such as ultrasound and molecular testing are crucial. The diagnostic approach is separated into two categories based on whether a family history is present or not.[13] In cases where a known family history of OI exists, the affected family is offered genetic counseling and diagnosis, and future parents may benefit from information on inheritance patterns (e.g., autosomal dominant or recessive). When there is no family history and ultrasound scanning reveals a decrease in femoral length in the second trimester, doctors typically assume fetal OI.[14]

Clinicians and radiologists diagnose patients with mild to moderate OI after birth. Even within the same family, the clinical signs of the mild form of OI can differ within the same mutation.[15] Differentiating mild onset osteoporosis or child abuse from osteoporosis might be challenging at times. Apart from the skeletal symptoms, there are impairments in several tissues that express type I collagen. These include blue-grey sclera, dentinogenesis imperfecta (which manifests as tooth discoloration from a dentin defect, missing permanent teeth, and malocclusion), young-adult onset hearing loss, muscle weakness, reduced respiratory function and cardiac valvular regurgitation.[16] Reduced muscle strength is linked to exercise intolerance, easy fatigability, and gross motor delay. In addition to fractures, bone abnormalities and ligamentous laxity may also contribute to reduced mobility, particularly in cases of severe OI.[17-19] The diagnosis of mild OI is also aided by these symptoms. Progressive bone malformations, like scoliosis, rib cage abnormalities, and long bone bowing, are seen in moderate-to-severe forms of OI.[4,20,21]

While growth deficiency and reduced growth velocity are also noted in the milder OI type I, short stature is a key characteristic in the moderate and increasingly deforming OI, types III–IV (even in the absence of substantial bone abnormalities).[22,23] Aortic root dilatation, valve dysfunction, and infrequently aortic aneurysm and dissection are among the cardiovascular symptoms associated with OI that have been documented.[2,24] In patients with OI, pulmonary problems are a significant source of morbidity and death. These issues can result from both increasingly known intrinsic lung abnormalities and extrinsic causes such as scoliosis, rib fractures, and muscular weakness.[25]

TREATMENT

There is currently no cure for OI. Depending on the patient's age, the disease's severity, and patient's functional status, different therapeutic strategies could be used. Reducing the frequency of fractures, reducing pain, and promoting growth, mobility, and functional independence are all objectives of treatment for OI. Multidisciplinary care should be given, integrating medical genetics, orthopedic surgery, physical therapy, dental expertise, and other subspecialties based on the symptoms and problems, since there can be various skeletal and extraskeletal manifestations.[26] Orthopedic care encompasses the therapy of long bone and spinal abnormalities through surgery as well as fracture repair.[2,21] Intramedullary rodding surgery may be necessary to straighten bowed femurs and tibias in severe cases of OI.[27,28]

In order to support motor growth, boost endurance, reduce pain, gain independence, and aid in the healing process following surgical operations, physical therapy and rehabilitation are crucial.[26,29] Nutritionally speaking, sustaining sufficient levels of calcium and vitamin D is critical to promoting bone health, as well as enhancing the effectiveness and reducing the side effects of using bisphosphonates.[2]

Antiresorptive Treatment

Bisphosphonates, which include zoledronic acid, risedronate, alendronate, and pamidronate, constitute the cornerstone of pharmaceutical management for pediatric OI patients. It has been demonstrated that bisphosphonates enhance bone mass and architecture while also somewhat lowering the risk of fracture. By causing osteoclast apoptosis and inhibiting osteoclast activity, they achieve their desired effect.[30,31] In growing children with OI, bisphosphonates have a significant effect on the vertebra throughout growth and can cause remodeling in cases of vertebral compression fractures.[1] They can be infused intravenously or given orally. According to recent research, intravenous bisphosphonates have a greater impact on BMD and fracture rate than oral bisphosphonates.[32,33]

Intravenous bisphosphonates also have improved absorption, adjusted dosage, reduced gastrointestinal side effects, and resulted in higher patient compliance. The most frequent adverse effects of bisphosphonates, which are normally well

tolerated, include gastrointestinal irritation when taken orally and an acute phase infusion reaction, which usually happens during the first infusion and manifests as hyperpyrexia, myalgia and weakness. Pretreatment with calcium and vitamin D can stop transient hypocalcemia.

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL), which is an osteoclast differentiating factor. It inhibits osteoclast formation, decreases bone resorption, increases BMD, and reduces the risk of fracture.[34] Children with SERPINF1, COL1A1, and COL1A2 mutations have been documented to benefit from denosumab treatment, which decreased bone turnover markers and increased areal BMD.[35,36] It is administered by subcutaneous injection. Atypical hip fractures, osteonecrosis of the jaw and hypercalcemia are among the side effects that have been reported.[34]

Growth hormone (GH) therapy-because of its possible anabolic effect on bone, GH has been suggested as a treatment for OI in order to address the growth shortage. According to a preliminary study, certain patients—mostly those with OI type IV—might respond to GH treatment by experiencing a little increase in cancellous bone density along with a rise in linear growth rate.[37] An additional study that contrasted bisphosphonates alone with GH and bisphosphonate therapy found a synergistic effect on growth velocity but no effect on fracture risk.[38]

Anabolic Treatment

The goal of osteo-anabolic therapy is to promote bone growth and osteoblast activity.[39] The first anabolic treatment authorized for use in osteoporosis was teriparatide, also known as recombinant human parathyroid hormone (PTH) 1-34. Osteosarcoma risk was enhanced by preclinical investigations conducted in rats treated with high doses of teriparatide.[40] As a result, it has not been used on pediatric patients and its clinical use is restricted to a 24-month period.

Targeting sclerostin, a glycoprotein that prevents bone formation by blocking the canonical Wnt signaling pathway in osteoblasts, is the goal of sclerostin-inhibitory antibodies (Scl-Ab/Romosozumab). The use of romosozumab in treating osteoporosis was recently approved. Sclerostin inhibition treatment has been shown in preclinical research using animal models of OI to have positive effects on bone formation and BMD.[31]

Transforming growth factor beta (TGFβ) inhibition aims to stop the over-activation of TGFβ signaling, which is connected to controlling bone fragility and mass in OI patients.[31,42,43] Preclinical research on mice with OI treated with TGFβ inhibitory antibody revealed enhanced bone mass and bone strength.[44]

Progenitor cell therapy – it has been suggested that OI's innate bone fragility can be specifically addressed by using progenitor cell therapy, which involves transplanting healthy progenitor stem cells. The rationale is that normal collagen is produced by osteoblasts, which are formed from engrafted healthy donor cells.[31] Although promising thus far, cell therapy is still in its experimental stages because of variable outcomes, safety issues, and ethical constraints.

Methods based on genetic engineering and somatic cells reprogramming into iPSCs (induced pluripotent stem cells)– aim to correct defects in genes. Currently there are multiple methods for modifying transcripts of collagen mutants. The latest method involves silencing or inactivating the mutant gene, resulting in allele suppression and haploinsufficiency, to transform the severe type of OI based on structural deficiencies in collagen I protein into a less severe quantitative form.[45] These techniques are still in the experimental stage, despite the intriguing outcomes.

Fractures and Deformities Treatment

Fractures in OI pediatric patients are treated similarly to those of typical children, while keeping the time of immobilization to minimum. Babies who are severely impacted typically have several fractures at birth, each in a different state of healing. Unstable fractures require a straightforward splint to help with nursing and to lessen pain. Painkillers could also be required and pain normally subsides as the fractures heals over a few weeks. Regular clinic evaluations during the first few months of life are crucial. Support can also be given with intramedullary rods. Although it significantly lowers the number of fractures in the affected bone, it has the drawback that when the bone grows, it bows past the rod and breaks again. Telescopic rod was invented to avoid these problems.[46] When severe cases of OI go untreated, scoliosis and kyphoscoliosis are frequently observed. Arthrodesis combined with spinal instrumentation is suitable in certain cases. However, the vertebral bodies flatten within the first few years of life and scoliosis develops quickly in many children with severe OI. Most of the time, orthotics or plasters are unpractical since the deformation of the chest wall occurs without altering the curve of the spine. The majority of internal fixation techniques are likewise inappropriate for the little and severely osteoporotic vertebrae.[47]

DISCUSSION

This literature review highlights the current challenges faced by clinicians when treating the pediatric population diagnosed with OI. In recent years, numerous additional genetic causes of OI have been discovered, despite the fact that COL1A1/A2 mutations account for the majority of cases. A few of these genes are involved in type I collagen processing. Nowadays we know more about the biomechanics of OI bone, including its material characteristics, the impact of muscle and gait stress, and how to handle fractured bones. With the use of suitable controls, biomechanical models may be able to assist in identifying activities that provide a higher risk of fracture and allow individuals with OI to engage in a wider range of activities in a safer and more comprehensive manner.

The presence of deformities and functional limitations is the keyaspect of OI. There is ongoing discussion in the literature regarding the proportion of patients who have limitations and/or deformities. Although Mrosk's study only included 50 patients, it revealed malformations in terms of bone bowing throughout the entire cohort.[48] In contrast, another study by Li at al.[49] revealed a lower rate of deformities and a higher prevalence of limitations.

Numerous non-bony symptoms of OI are common, affecting various organs and systems and having an effect on the lives of

the patients. Assessing if those characteristics are present in a sizable OI population could provide clinicians with insightful input on how to carry out a diagnostic procedure and treatment. In addition, because of the great variation in type, length, administration method, age at treatment, etc., statistics on drug treatment are sometimes imprecise and challenging to assess and compare.

An essential component of these patients' care is physical therapy. Children with moderate to severe OI are frequently treated with intravenous bisphosphonates. Some of the benefits seen in observational studies have been hard to prove in controlled studies. Other viable OI therapies are being researched. Overall, further research is necessary to understand the precise mechanism and clinical consequences of abnormalities in individuals with OI.

Taking all of the above into consideration, the strength of this study is reflected in highlighting current gaps in knowledge related to the treatment of this condition, and possible future trends in dealing pediatric patients with OI. Limitation of this overview is a lack of systematic searching methods and evaluation. Partial influence of the author's own perspectives and opinions expressed in this review article could be considered as a limitation of this study, in the context of bias.

CONCLUSION

OI is an uncommon multisystem disease with variable clinical characteristics and severity that is typified by primary bone fragility. Children who have OI may require orthopedic and other surgeries on many occasions. The most common causal mutations are on COL1A1 and COL1A2, while more genes have recently been found to contain alterations. The current OI therapy approaches focus on increasing bone mass, managing symptoms, and preventing fractures. Bisphosphonates, denosumab and GH are the three types of drugs most frequently utilized in the treatment of OI in pediatric patients. The main disadvantage of these therapies is their relatively weak efficiency, the lack of effects in some patients or cytotoxic side effects. Genetic engineering and stem cell transplantation are promising approaches for treating OI and other genetic bone diseases in the future.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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