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A Narrative Review on Osteogenesis Imperfecta and Its Management

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Abstract

Osteogenesis imperfecta (OI), sometimes referred to as brittle bone disease, is a heterogeneous illness characterized by short stature, several fractures, and distorted bones. The main contributing factor to OI is mutations in the genes needed to produce type 1 collagen. While severe OI is perinatally fatal, mild OI can occasionally not be detected until maturity. The frequency of Osteogenesis imperfecta ranges from about 1:15,000 to 1:20,000 births. Five kinds of the illness are commonly differentiated, ranging in severity from moderate (type I) to deadly (type II). Types III and IV are serious types that permit survival during the newborn period, but type V has a mild to moderate phenotype and interosseous membrane calcification. The majority of the time, mutations in the col I genes result in a decrease in the production of common type I collagen (col I) or the synthesis of uncommon collagen. Moreover, it has been shown that mutations in the genes responsible for osteoblast development, col I processing, and synthesis have occurred. The objective of this study is to review the research on the current medical treatments for osteogenesis imperfecta (OI) in patients. The treatments that are currently available aim to reduce or eliminate symptoms, prevent fractures, and build bone mass. Medications like bisphosphonates, denosumab, and teriparatide are frequently used to treat OI.

Keywords: Osteogenesis imperfecta, bisphosphonates, denosumab, teriparatide, physiotherapy

INTRODUCTION

A collection of inherited skeletal illnesses with a broad range of appearance is called osteogenesis imperfecta (OI), often known as brittle bone disease [1, 2]. The central feature of OI is the skeletal fragility and its predisposition to fractures as a result of structural and or quantitative abnormalities of collagen, especially, type 1 collagen found in bones, teeth tendons, ligaments, skin and sclerae [1]. Several genetic defects have been identified, as well as the different defective proteins. These discoveries have necessitated further genetic classification of OI in addition to an original clinical classification that describes OI syndromes [3–6]. At present, there are five clinical syndromes, which are mostly inherited in an autosomal dominant (AD) pattern and 20 genetic subtypes with various modes of inheritance [5, 7]. The incidence of osteogenesis imperfecta (OI), an uncommon skeletal abnormality, ranges from 1/15,001 to 1/20,000 [8]. A high incidence of fractures, bone fragility, inadequate growth, and bone abnormalities are kind of Osteogenesis imperfecta [9]. People with OI may also develop other clinical symptoms such brittle teeth, blue sclerae, hearing loss, reduced respiratory function, and heart valve regurgitation because type I collagen formation in numerous tissues is impeded [9]. The most severe form of OI, which is perinatally deadly, can range in intensity from mild to extremely severe [10]. Osteogenesis imperfecta is clinically classified using the Silence scale, which initially identified four categories of Osteogenesis imperfecta based on their clinical presentation [11].

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These “classical” Osteogenesis imperfecta kinds are connected with autosomal mutations in the genes encoding type I collagen (COL1A1, COL1A2) and still account for 85 to 90% of Osteogenesis imperfecta cases [12]. In contrast to structural mutants, haploinsufficiency, which reduces collagen production, often results in milder types of OI. These mutations cause qualitative or structural flaws in the collagen protein [13, 14]. This system of classification has been broadened to incorporate mutations that have been found in a variety of genes that are dominant, recessive, and X-linked. It is possible for non-collagen mutations to cause non-classical OI phenotypes that exhibit distinctive clinical traits, such as the hyperplastic callus formation observed in type V Osteogenesis imperfecta [15]. The present approach to treating Osteogenesis imperfecta concentrates on lowering the risk of fracture, improving motor function, escalating inclusion, and improving quality of life. This requires a multidisciplinary approach from a variety of healthcare providers, including medical doctors, orthopedic surgeons, physiotherapists, geneticists, and other allied health professionals [16]. Antiresorptive medications have been shown in numerous studies to enhance bone mass and lower total risk of fracture, especially in younger populations [17–19]. Notably, medications like bisphosphonates cause increases in bone volume rather than improving the material qualities of bone (i.e., improving bone quality). This results in relative gains in strength.

Classification

OI has historically been categorized in accordance with Sillence, who in the late 1970s established a revised categorization system based on radiological, clinical, and genetic data (Table 1) [20–22]. Sillence type I refers to the mildest and most prevalent kind of OI. Fractures, blue sclerae, and hearing loss are all connected to this kind. These people frequently suffer from many fractures as children, but their clinical conditions improve during puberty and they have a typical life expectancy [23]. The perinatal deadly variety of OI is type II. Infants and fetuses who are affected are frequently stillborn or pass away shortly after birth as a result of many thoracic fractures complicating breathing and perhaps having an intrinsic pulmonary collagen disease [24]. The most serious Osteogenesis imperfecta kind that can endure the newborn period is type III. Numerous fractures may be sustained by OI type III patients, who also frequently have a noticeably small stature, increasing deformities, severe scoliosis, and a condensed lifespan [25–30]. DI is typical, and the hue of the sclera can vary. Sillence type IV is a medium variety, with phenotypes that fall between types I and III in terms of seriousness and clinical traits. The Sillence system of classification is commonly used, although it has currently been complicated by the variation in underlying genetic background and the phenotypic variability of collagen I mutations [31–38]. Every new gene that has been found to create an OI-like phenotype has been given a Roman number, and there are currently 17 types that have been identified (Table 1) [39]. There is no clear agreement on how to identify and categorize this disorder, and the Osteogenesis imperfecta phenotypes brought on by non-collagenous genes overlay with those brought on by conventional dominant OI produced by collagen I mutations [40–49].

PATHOPHYSIOLOGY

The majority of OI patients have an autosomal dominant mutation in COL1A1 or COL1A2, which encode the α1(I) and α2(I) chains of type I collagen, respectively. More than 1500 dominant mutations in the COL1A1 and COL1A2 genes have been discovered so far [50–52]. A lack of type I collagen either structurally or quantitatively results from these mutations [52]. Quantitative deficiencies have a milder phenotype than structural and qualitative problems [53]. The most common protein in connective tissue's extracellular matrix is collagen [54]. The triple helix-shaped structure of collagen molecules is made up of three polypeptide chains. For the synthesis of the triple helix, glycine is necessary, as only glycine can fit the partial internal helical space [53]. Type I collagen develops structural and functional flaws when a gene mutation results in glycine replacement, which disrupts helical flossing [55]. In contrast to substitutions in the α2(I) chains, which are often non-lethal, those in the α1(I) chains have lethal effects [52]. On the other hand, the mildest form of OI is caused by haploinsufficiency of COL1A1, which reduces the production of structurally normal collagen [56]. A normal phenotype is produced by COL1A2 haploinsufficiency, whereas homozygous null mutations of COL1A2 result in

phenotypes that range from mild to severe Osteogenesis imperfecta. In addition, IFITM5 (interferon inducible transmembrane protein family 5), commonly known as BRIL, has another unusual autosomal dominant mutation [57]. The bone's ability to mineralize and differentiate is inhibited as a result of this mutation [58]. The majority of Osteogenesis imperfecta cases are caused by dominant or sporadic mutations [59]; however, in the past two decades, uncommon autosomal recessive or X-linked mutations have also been discovered [53]. These genes are involved in the osteoblast synthesis (e.g., WNT1, CREB3L1, and SP7), ossification or mineralization (e.g., SERPINF1), extracellular post modification of collagen (e.g., CRTAP, LEPRE1, and PPIB), and collagen folding and intracellular trafficking (e.g., SERPINH1 and FKBP10) [53, 58].

EPIDEMIOLOGY

Osteogenesis imperfecta has a birth rate of 6–7/100,000. The incidence and prevalence of the various OI types vary, with Osteogenesis imperfecta types I and IV making up significantly more than half of all Osteogenesis imperfecta cases [60]. Sillence *et al*. observed a prevalence of 3–4/100,000 and an incidence of 3.5/100,000 for Osteogenesis imperfecta type I in Victoria, Australia. Due to early fatality, data on prevalence for OI type II are not available, however the frequency is approximately 1–2/100,000 [60]. The incidence of OI type III is 1–2/100,000. In Australia, an incidence of 1.6/100,000 has been recorded [3]. OI type IV was thought to be an uncommon phenomenon, but this proved not to be the case [60].

Table 1. Classification of osteogenesis imperfecta types.

Types of Osteogeneses	Phenotype	Gene Affected
Dominant inheritance classical Sillence types		
I	Mild, nondeforming	COL1A1 or COL1A2
II	Perinatal lethal	COL1A1 or COL1A2
III	Progressively deforming	COL1A1 or COL1A2
IV	Moderately deforming	COL1A1 or COL1A2
COL1-mutation negative		
V	Moderate, distinct histology and hyperplastic callus	IFITMS
XV	Mild/early onset osteoporosis	WNT1
Recessive inheritance Mineralization defect		
VI	Moderate to severe, distinct histology	SERPINF1
3-Hydroxylation defects		
VII	Severe to lethal	CRTAP
VIII	Severe to lethal	LEPRE1
IX	Moderate to lethal	PPIB
Chaperone Defect		
X	Severe	SERPINH1
XI	Progressive deforming, Bruck Syndrome	FKBP10
Zinc-finger transcription factor defect		
XII	Moderate	SP7
C-Propeptide cleavage defect		
XIII	Severe high bone mass case	BMP1
Cation Channel defect		
XIV	Moderate to severe	TMEM38B
WNT signaling pathway defect		
XV	Moderate, progressively deforming	WNT1
Unclassified ER stress transducer deficiency X-linked inheritance	Severe	CREB3L1
Unclassified suspected osteocyte defect	Mild	PLS3

MANAGEMENT

Pharmacological Treatment

For OI, current therapy options include managing symptoms, increasing bone mass, and preventing bone fractures. Both non-surgical and surgical techniques are used to treat OI. The non-surgical approach involves the use of medicines, physical therapy, braces, and splints to stay away from deformity and to enhance protection and support. In order to treat local diseases such scoliosis, bone bending, or fractures, surgery may be necessary. In order to typically combat the systemic effects, medication must be taken. Since the primary publication of the effect of bisphosphonate treatment in children with serious OI, intravenous and oral bisphosphonates are routinely prescribed for all Osteogenesis imperfecta kinds, elders as well as kids [61] The main justification for bisphosphonate medication is based on several (not placebo-controlled) clinical trials that showed increases in bone mineral density in OI patients. Non-nitrogenous bisphosphonates trigger osteoclast apoptosis, while nitrogenous bisphosphonates interfere with osteoclast development, survival, and cytoskeletal dynamics. According to a newly published systematic evaluation of bisphosphonate treatment in Osteogenesis imperfecta [62], there is a considerable improvement in bone mineral density in a relatively limited proportion of patients who have OI and are receiving intravenous or oral bisphosphonates. The most necessary query that has arisen, however, is whether rise in bone mineral density leads to a decrease in fractures and an improvement in function; this subject has not yet been addressed and calls for further research [62]. The use of growth hormone to reduce short stature in types III and IV Osteogenesis imperfecta [63] is presently being researched [64]. Denosumab is a monoclonal antibody (IgG2) that targets RANKL, a nuclear factor kappa-B ligand that inhibits the synthesis of osteoclasts without attaching to bone [65]. The benefit of Denosumab is a relatively brief degradation period, which lasts for 3 to 4 months, avoiding the long-term accumulating negative effects of BPs [66]. This compound has demonstrated promising results with a comparatively high level of safety when investigated in patients with OI types I, III, IV, and VI who are not sensitive to BPs [66, 67]. Additionally, after 10 years of therapy with Denosumab in postmenopausal women with osteoporosis, studies from the major, phase III clinical FREEDOM trial showed persistent increases in bone mineral density with only low rates of side events and a low fracture incidence [67, 68]. In addition, there have been reports of hypercalcemia, hypercalciuria, and rebound symptoms after quitting the medication for Denosumab [69]. These reports suggest that more research on this substance is still needed. In a randomized controlled trial, the bone anabolic drug teriparatide was evaluated in people with Osteogenesis imperfecta [70]. In mild Osteogenesis imperfecta, there was an increase in BMD, but it was less effective in moderate-to-severe Osteogenesis imperfecta. According to these results, teriparatide showed beneficial effects in two studies that targeted individuals with Osteogenesis imperfecta type I [71, 72]. Teriparatide may therefore be effective in the management of mild Osteogenesis imperfecta in elders. However, teriparatide should not be used in youngsters, though, as research in developing rats has linked it to an elevated risk of osteogenic sarcoma [73].

Gene and Cell Therapy

The two ways by which mutations are reduced in nature, silencing a mutant allele and cellular mosaicism, are emulated in the most potential future treatments for OI caused by faulty collagen structure. To mimic the scenario in type I OI where the mutant allele is quiet, many gene-silencing approaches (ribozymes, small interfering RNA, and short hairpin RNA) have been examined *in vitro* [74]. Instead of curing OI, this strategy would cause a milder OI. Although these methods can produce silencing that is nearly complete in a test tube, the silencing in cells is typically incomplete, and the duration of the impact is constrained. The condition in mosaic parents of Osteogenesis imperfecta kids, who have two populations of cells (nonmutant and mutant), and rarely seek medical assistance before the birth of their child, is mimicked by cell transplantation. Cell absorption into bone has been a problem for this strategy. Despite stem cell uptake being less than a little percentage points, studies in mouse models used enhanced bone mechanics [75, 76]. Green fluorescence protein (GFP)-tagged cells have been retransplanted to a secondary recipient, demonstrating their survival, and higher levels of cell transplantation have been achieved with local transplantation more recently [77]. Fetal mesenchymal

stem cells are being transplanted *in utero* or during the first few months after birth in a clinical experiment now taking place in Europe.

Surgical treatment

Reducing pain and ensuring recovery without a rise in abnormalities are the two main goals of orthopedic operations in the treatment of patients with OI. Conservative therapy with a cast is frequently sufficient for fractures without dislocation or in individuals whose bone is aided by an intramedullar rod. Children who have severe long bone abnormalities that might prevent verticalization or limit the functional use of the higher extremity should undergo surgical therapy to repair the deformities. Intramedullar telescopic rods ought to be implanted throughout growing. These grow longer during development and can support the bones for a very long time [78]. It should be highlighted that extended immobilization is not necessary for individuals with classical Osteogenesis imperfecta caused by mutations in COL1A1/2 because these patients' fractures heal just as quickly as those in unaffected people. Healing might be modified in some uncommon types. For instance, this may occur in individuals with mutations in IFITM5 (hyperplastic callus formation) or WNT1 (delayed healing). To avoid muscular atrophy and subsequent bone resorption brought on by immobility, prolonged immobilization must be avoided.

Physiotherapy Management

From the time an OI individual is diagnosed, the physiotherapist plays a critical part in their care. Depending on the seriousness of each individual condition, they can help parents of early Osteogenesis imperfecta babies and kids with safe positioning and handling of the child and setting realistic aims for achieving developmental milestones. Among these milestones, the capacity of the child to move independently, whether with help from a walker or later a wheelchair, is probably the most important. To improve the musculoskeletal health of children with Osteogenesis imperfecta and support their transition into independent adulthood, the physiotherapist's long-term engagement is essential. There is proof from observational research that supervised exercise programs can improve physical capacity and muscle strength [79, 80]. According to anecdotal evidence, strengthening muscles may help individual with hypermobility, a typical symptom of Osteogenesis imperfecta, stabilize their joints. Persons with Osteogenesis imperfecta have a propensity to be discouraged from engaging in sports, yet there are several instances of persons with Osteogenesis imperfecta succeeding in their chosen sports. This can then enhance quality of life and general well-being. Many individuals are hesitant to try novel movement patterns due to recurrent fractures, which should be taken into account throughout training. Additionally, as muscles get stronger, an osteoanabolic signal is triggered, which causes osteoblasts to produce more extracellular matrix. Utilizing the muscles is still the greatest strategy to induce bone growth even though OI can decrease osteoblast activity [81].

CONCLUSION

OI has evolved over the past few decades from a condition with an unidentified etiology to a disorder with a thoroughly characterized and mapped genetic background. Medications such as bisphosphonates, denosumab, and teriparatide are used to treat people with OI; among these, bisphosphonates are the most promising therapy for promoting bone formation by inhibiting bone resorption. Surgery guarantees a reduction in pain and recovery without worsening of abnormalities. Timely remobilization and consistent muscle strengthening through physiotherapy are crucial for improving mobility, preventing bone resorption, and avoiding muscle wasting due to immobilization. However, the majority of these strategies are still in the testing phase. Further research is therefore required to verify their therapeutic advantages in osteogenesis imperfecta.

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Asad Jamal Ansari completed the main writing, drafted the article, and collated the reference with Md Nematullah. Guisia Khan and Kudshiya Khan guided the frame construction of the article and took

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Declaration of Competing Interest

None.

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Data sharing does not apply to this article as no new data were created or analyzed in this study.

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