Review Article

Jour Cas Stu Cas Rep, 2(2), 2023, 28-32

Journal of Case Studies and Case Reports

Open access peer reviewed international indexed journal Online ISSN: 2583-4428

Content Available at www.saap.org.in

REVIEW ON: OSTEOGENESIS IMPERFECTA

Megavath Vathinelu Naik*, Srungarapu Yashodhar Reddy, Chandu Babu Rao and Ponnaganti Mohan Vikas

Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, Pulladigunta-522017, Guntur, Andhra Pradesh. India.

Received: 20 July 2023 Revised: 21 July 2023 Accepted 28 Aug 2023

Abstract

A rare congenital illness known as osteogenesis imperfecta (OI) can range widely in severity and is marked by additional, variable extra-skeletal symptoms along with increased bone fragility and skeletal deformities. Here, we provide a summary of the pathophysiological underpinnings, genetic heterogeneity, and current therapy options for OI-related bone fragility disorders. Mutations in the two collagen type I genes are the cause of the most prevalent type of OI. While missense mutations mostly cause structural changes in the collagen protein and result in a more severe phenotype, stop mutations typically result in decreased collagen quantity and a milder phenotype. prescription drugs.

***Keywords*:** Osteogenesis imperfecta, Pathophysiology, Genetic heterogeneity, Therapy, Bisphosphonates.

***Corresponding Author**
Megavath Vathinelu Naik

doi: https://doi.org/10.37022/jcscr.v2i2.603

Introduction

Osteogenesis imperfecta (OI) is an inherited collagen type 1 disorder with varying clinical manifestations.(1,2) Hallmarks include bone fragility, blue sclera, impaired hearing, defective dentition and hyperlaxity.(1,3) The diversity of age at presentation and bone fragility best demonstrate the broad clinical spectrum of this condition.(2) The clinical presentation ranges from mild forms to severe and lethal forms. 1,2 Milder forms generally present in later stages of life(3), often with long bone fractures after minor trauma while the more severe forms can present with marked skeletal Dysplasias, delayed milestones and even perinatal or early childhood death.

Epidemiology:

The subtypes of OI diverge in both their incidence and prevalence rates, with OI types I and IV comprising more than half of all total cases worldwide(10).5 The global incidence of OI is approximately one per 20 000 live births and the prevalence is about six to seven per 100 000. There is a relative paucity of literature on the incidence and prevalence of OI in South Africa. Beighton et al. found an estimated minimum population frequency of 0.6/100 000 for OI type III in the black African population residing in the Johannesburg region and 0.1/100 000 for OI type I in the same group.(6) However, in the Southern African indigenous population, OI type III tends to occur with greater frequency compared to other geographical regions.

Symptoms:

The symptoms of the disease can be divided into skeletal and extra skeletal findings. Skeletal symptoms are the decreased bone mass leading to reduced bone stability. This resultsin an increased fracture rate of the long bones after inadequate trauma, as well as deformities of vertebrae. Scoliosis is an additional problem that develops frequently during puberty in more severely affected patients and can lead to an impairment of the pulmonary function. Short stature is present in almost all patients and extremities can be disproportioned. There may alsobe axis deviations and differences in length of the long bones.

As a collagen disorder, additional extra skeletal symptoms can include hypermobility of ligaments and enlarged fragility of vessels. An impact on heart valves has also been describedas well as an early hearing loss. An obvious but not always persistent finding is a blue Gray discoloration of the sclera in approx. 50% of OI patients. Due to the close biochemical relationship between collagen and dentin, the teeth are affected in some patients leading to dentin oogenesis imperfecta with be collared appearance and increased brittleness.

Classification:

Type	Severity	Features	Inheritance
I	Mild	Blue sclerae, mild bone fragility, fractures after walking, minimal deformity	Autosomal dominant or new mutations
II	Lethal	Blue sclerae, multiple intrauterine fractures, severe deformity, stillbirth or neonatal death	Autosomal recessive or new mutations
III	Severe deforming	Normal sclerae, dentinogenesis imperfecta, frequent fractures, deformity of long bones, short stature, scoliosis	Autosomal recessive or new mutations
IV	Intermediate	Normal sclerae, moderate bone fragility, moderate deformity, short stature, possible dentinogenesis imperfecta	Autosomal dominant or new mutations

Classification of osteogenesis imperfecta:

In 2006, the first genetic cause of autosomal recessive lethal OI was discovered, i.e. bi-allelic variants in the CRTAP gene causing complete loss of protein function [Barnes et al., 2006]. Partial loss of function CRTAP variants encoding cartilage-associated protein (CRTAP) were found to cause OI type VII [Morello et al., 2006]. Presently, 6 more causes of recessive OI (causative variants in LEPRE1 [Cabral et al., 2007], PPIB [Van Dijk et al., 2009b; Barnes et al., 2010], SERPINH1 [Christiansen et al., 2010], FKBP10 [Alaney et al., 2010], SP7 [Lapponian et al., 2010], and SERPINF1 [Becker et al., 2011]) have been described, all but 2 (SP7 and SERPINF1) concerning genes encoding proteins involved in collagen type I biosynthesis.

Pathogenesis:

Osteogenesis imperfecta, also known as brittle bone disease, is a rare genetic heterogeneous connective tissue disorder with an incidence of 1 in 15,000 to 20,000 newborns. The skeletal phenotype of patients with OI is characterized by reduced bone density, increased bone fragility, recurrent fractures, and progressive skeletal deformities. More common extra skeletal phenotypes include blue sclera, Dentino genesis imperfecta, and hearing impairment. In the past, OI was thought to be caused only by dominant mutations in the genes encoding type I collagen (COL1A1 and COL1A2) resulting in defective type I collagen, and patients with OI were classified as Sillence types I-IV based on the clinical phenotype.(5)

Phenotypes and genotypes of OI:

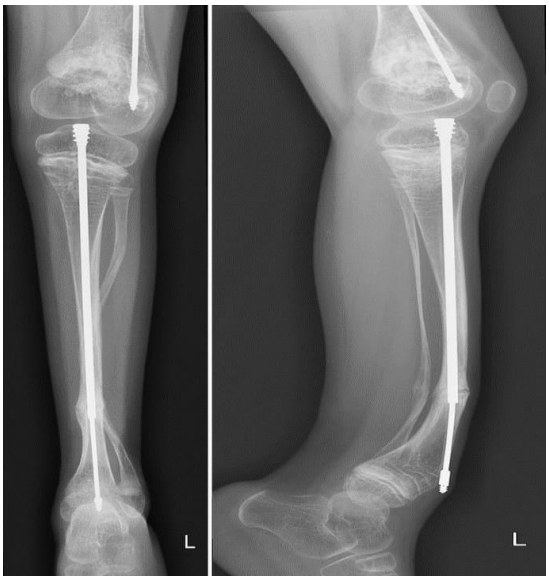

Figure 1 (A, B) Radiologic demonstration of marked differences in phenotype: OI types I and III.

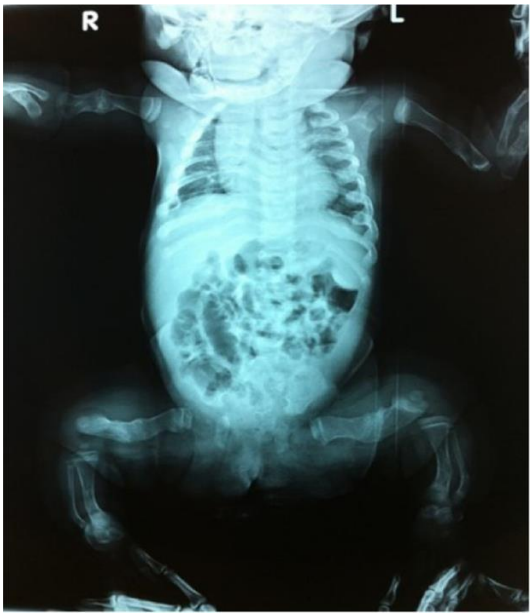

Fig.2 OI type III, 2-month-old baby girl.

It functions in bone homeostasis and osteoid mineralization. Affected individuals have a moderate-to-severe OI, presenting decreased bone mineral density (BMD) with no fractures atbirth and without blue sclerae or DI. Bone biopsy shows a characteristic “fish-scale” pattern caused by disorganization of the bone matrix, with large amount of unmineralized osteoid tissue simulating osteoma Lacia.

Individuals with OI types VII, VIII, and IX have severe to lethal phenotypes caused, respectively, by mutations in the *CRTAP*, *LEPRE1*, and *PPIB* genes. Approximately 1.5% of

West Africans and 0.4% of African Americans carry a founder mutation in *LEPRE1* gene andthree lethal cases of OI-VIII were reported in individuals of these ethnicities.(18,19) In addition to

features common to severe OI phenotypes, mutations in *CRTAP* and *LEPRE1* genes (OI-VII, OI-VIII) are associated with formation of bulbous epiphysis with popcorn calcifications at thedistal femurs. A homozygous mutation in *TMEM38B* gene is associated with OI type XIV, which appears to be an ancient mutation in Israeli Bedouin and Saudi families from the Arabian Peninsula.

Mutations in *WNT1* gene are related to OI-XV. Components of the canonical Wnt/β-catenin signalling pathway are integral for normal osteoblast differentiation as well as the differentiation of several types of stem cells. Fahimi Niya et al have reported *WNT1* mutationsin four children from three families. These children had short stature, low bone density, and multiple vertebral compression fractures in addition to multiple long-bone fractures during the first years of life. A homozygous nonsense mutation was identified in two siblings, this led to brain malformation and severe intellectual disability not associated with major OI phenotypes.

SPARC (OI-XVII) is the gene most recently associated with an OI phenotype. Two distinctive homozygous missense

mutations in *SPARC* were reported from two unrelated girls with severe bone fragility. Besides severe bone fragility, one had severe early-onset scoliosis requiring spinal fusion at age 6 years. The second girl was born prematurely of a consanguineous couple, with hypotonia and gross motor developmental delay. Histomorphometry study showed matrixhyper mineralization.

Management /treatment:

The mainstay of OI management is orthopaedic surgery when needed and rehabilitative physiotherapy (8). The optimal care environment would be a specialized multidisciplinary clinic. Promoting general physical wellbeing is an important aspect of OI management and must be initiated from a very early age. General fatigue during daily activitiesis a common complaint and because muscle strength and exercise tolerance is reduced in OI, maintaining physical health is paramount to good general health.

Medical treatment:

Medical treatments with bisphosphonates are currently used as standard therapy in patients with a moderate or severe course in childhood and adolescence. Upon administration bisphosphonates bind to the hydroxyapatite crystals of the bone, which are resorbed by osteoclasts during bone remodelling and induce their apoptosis. These drugs effectively reduce bone resorption and thereby increase bone mass. Bisphosphonates are ap proved for the therapyof geriatric osteoporosis and dosing and treatment intervals are adapted to the pediatric needs. It has been shown that intravenous therapy has a positive effect on skeletal pain and bone mass, and in addition, mobility of patients can be improved (5). Different bisphosphonates (pamidronate, etidronate, zoledronate) have also been used and differ in treatment intervals.

Oral bisphosphonates are less effective but can also be used in special indications. Treatment must be carried out regularly and should continue during growth (7). Despite a broad consent about the beneficial effect of bisphosphonates in moderate or severely affected children a reduction of fractures was never shown in this population (8). It has to be mentioned that bisphosphonates are not approved for children in Germany and many other countries and can only be administered as "off-lable-use" after careful discussions and written consent.

Orthopaedic intervention:

The aim of any orthopaedic intervention is to optimise function, avoid or remedy any deformity and to monitor for any potential complications of OI. Care must be tailored to the individual patient. In milder forms, orthopaedic management rarely goes beyond conservative measures. Furthermore, the orthopaedic surgeon is rarely, if ever, called to assist in OI type II (perinatal death). It is the more moderate-to-severe phenotypes (OI types III to V)that often require specialised orthopaedic care.

Closed treatment techniques are the mainstay of fracture management. Fractures heal with abundant callus but with incremental deformities predisposing to further fracturing. Avoiding prolonged immobilisation and heavy splints is essential. Early mobilisation is actively encouraged.

Post-operative pain management may also be challenging, as many of the children may have been exposed to analgesics throughout their lives. Spasms are often a major component of post- operative discomfort and therefore short-term, low-dose diazepam may be beneficial.

The goals of surgery are the attainment and maintenance of optimal alignment with total correction of the deformity using an intramedullary rod which will act as an internal splint. As intramedullary rods are load-sharing, their misuse can result in stress-shielding.

With the Sofield-Millar technique, the individual fragments should be as long and as straight as possible. Placement of osteotomies in diaphyseal regions enhances stability with intramedullary rods. Some bone shortening may be necessary when there are severe deformities, as the taut soft-tissue structures on the concave side can be stretched excessively when a deformity is corrected. Reaming may be necessary for rod placement.24 Violation of the growth plate should be avoided. Immobilisation until union is almost always necessary.

Various techniques have been described for deformity correction, including closed reduction with traction followed by pneumatic splints (Morel technique), closed reduction with percutaneous intramedullary nailing, multiple corrective osteotomies with both non telescopic (Sofield-Millar technique) and telescopic intramedullary rods (Bailey-Dubow, Sheffield, Fassier-Duval, etc.). With each of these having their own advantages and pitfalls, surgeonpreference will guide decision-making.

In 1959, Sofield and Millar described their technique of sub periosteal exposure and multiple osteotomies (fragmentation) of a long bone deformity within the diaphysis and affixing these

fragments onto an intramedullary rod (shish-kebab). They used static intramedullary rods (Rush rods, K-wires, etc.) which proved to be very successful. This revolutionised the operative management of these severely deformed long bones, improving the mechanical characteristics of the bone and helping prevent further deformity and decreasing the risk of refractures. However, the children outgrew their rods, and complications such as rod migration were common (19).

In 2003, the Fassier-Duval telescopic rod was introduced as having the advantage of a single proximal entry point and improved 'screw-in' fixation in the epiphyses plus a revision rate of 14%.24 It is inserted through small incisions under fluoroscopic control in conjunction with percutaneous osteotomies, whenever possible.1,23-26 Rigid post-operative immobilisation is unnecessary.24,26 The procedure requires meticulous technique and

experience.24,26 Moreover, multiple bones may be treated simultaneously, reducing the operative burden on patients.

Surgical treatment:

Orthopaedic procedures have two main objectives in the treatment concept of patients with OI—to reduce pain and ensure healing without an increase of deformities. In case of fractures without dislocation or in patients in which the bone is supported by an intramedullary
rod, conservative treatment with a cast is often sufficient. In severely affected children with deformities of the long bones, which might prevent verticalization of the patient or restrict the functional use of the upper extremity surgical treatment with correction of deformities is specified. During growth, intramedullary telescopic rods should be inserted. These elongate during growth and can support the bones for many years (20).

It should be noted that fractures in patients with standard OI caused by mutations in COL1A1/2heal just as quickly as in non-affected individuals, and therefore, prolonged immobilization isnot required. In some rare types, healing might be altered. For example, this might occur in patients with mutations in IFITM5 (hyperplastic callus formation) or WNT1 (delayed healing).A long immobilization needs to be avoided in order to prevent muscle wasting and consequently resorption of bone mass due to immobilization.

Physiotherapy:

Medical and surgical treatments aim to improve the quality of life, mobility, and independence of patients. Many patients are also affected by a muscular hypotonia and weakness of tendonsand ligaments. Regular strengthening of the muscles is crucial to improve mobility. In addition, children have to learn which motor functions are possible after surgery. If deformities of the long bones have been corrected at the age of 2–3years, the older child has then to learn weightbearing and standing, and it has to be determined which assistive de vices are suitable to improve mobility(22).

Because of recurrent fractures, many patients are afraid to try new movement patterns, which must be taken into account during training. In addition, the strengthening of muscles induces an osteoanabolic stimulus, which leads to an increase in the synthesis of extracellular matrix
by osteoblasts. Although the function of osteoblasts can be impaired in OI, using the muscles is still the best way to stimulate bone formation.

Conclusion

A wide range of clinical manifestations are associated with osteogenesis imperfecta. It is one of the most prevalent congenital bone abnormalities that orthopaedic surgeons see, despite its rarity. There are significant variations in the patterns of the prevalence of specific sub-types, notwithstanding the dearth of accurate epidemiological data for sub-Saharan Africa. There is still no unanimous agreement, despite the fact that the classification has changed considerably since Sillence's initial definition. Sillence is in favor of the updated classification scheme that the International Nomenclature group for Constitutional Disorders produced, and more people are starting to use it, particularly in research communication. Particularly in a situation with limited resources like ours, being aware of the more nuanced clinical and radiographic characteristics of OI helps distinguish it from other metabolic bone diseases and aid in diagnosis. A surgeon specializing in orthopaedics who is knowledgeable about the fundamental sciences underlying this illness is better suited to treat it and prevent the tragic consequences that often accompany it. A multidisciplinary approach is still the cornerstone of comprehensive and long-lasting beneficial outcomes and is becoming more and more popular in our environment, even though newer medical, surgical, and rehabilitative therapies show great promise for the future.medication phenotype.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

References

1. Makareeva E, Mertz EL, Kuznetsova NV, Sutter MB, DeRidder AM, Cabral WA, Barnes AM, McBride DJ, Marini JC, Leikin S. Structural heterogeneity of type I collagen triple helix and its role in osteogenesis imperfecta. Journal of biological chemistry. 2008 Feb 22;283(8):4787-98.
2. Bachrach LK. Consensus and controversy regarding osteoporosis in the pediatric population. Endocrine Practice. 2007 Jan 1;13(5):513-20.
3. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, Widmer A, Devogelaer JP, Kaufman JM, Jaeger P, Body JJ. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. New England Journal of Medicine. 2002 Feb 28;346(9):653-61.
4. Zeitlin L, Rauch F, Plotkin H, Glorieux FH. Height and weight development during four years of therapy with cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta types I, III, and IV. Pediatrics. 2003 May 1;111(5):1030-6.
5. Vijayalakshmi, P; Girish, Ch; Mentham, Ramesh; Rao, Chandu Babu; Nama, Sreekanth; 2014. A REVIEW ON ALZHEIMER'S DISEASE. International journal of pharma and biosciences.IJPBS |Volume 4| Issue 2|APR-JUN|2014|19-27 https://www.ijpbs.com/ijpbsadmin/upload/ijpbs_536f304fa5e38.pdf
6. Sakkers R, Kok D, Engelbert R, van Dongen A, Jansen M, Pruijs H, Verbout AB, Schweitzer D, Uiterwaal C. Skeletal effects and functional outcome with

olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. The Lancet. 2004 May 1;363(9419):1427-31.

7. Shaik S, Suryaprabha M, Baburao C, Sreekanth N, Irfan P, Harshavardhan P, Pisipati SV. Featal alcohol syndrome. International Journal of Research in Pharmacy and Chemistry. 2012;2(2):371-5.
8. Dey B, Hwisa NT, Khalf AM, Mitra A, Katakam P, Rao CB. Pharmaco-epidemiological Studies on Self Medication and Drug Utilization Pattern in Chronic Diseases via Prescription Auditing. International Journal of Scientific Research in Knowledge. 2013 Nov 1;1(11):464.
9. De Coster PJ, Cornelissen M, De Paepe A, Martens LC, Vral A. Abnormal dentin structure in two novel gene mutations [COL1A1, Arg134Cys] and [ADAMTS2, Trp795-to-ter] causing rare type I collagen disorders. Archives of oral biology. 2007 Feb 1;52(2):101-9.
10. Kumar KR, Nagaraju GV, Subrahmanyam SN, Nagarani K, Shareef S, Tennygilphin M, Namballa M. Assessment on Elements Involving the Academic Performance among Pharmacy Students: A Cross-Sectional Observational Study. Int J Cur Res Rev| Vol. 2021 Dec;13(23):141.
11. Biran Y, Masters CL, Barnham KJ, Bush AI, Adlard PA. Pharmacotherapeutic targets in Alzheimer's disease. J Cell Mol Med. 2009 Jan;13(1):61-86. doi: 10.1111/j.1582-4934.2008.00595.x. Epub 2008 Nov 18. PMID: 19040415; PMCID: PMC3823037.
12. Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M, Tatò L. Intravenous neridronate in adults with osteogenesis imperfecta. Journal of Bone and Mineral Research. 2003 Jan 1;18(1):126-30.
13. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, Wesolowski G, Russell RG, Rodan GA, Reszka AA. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. Proceedings of the National Academy of Sciences. 1999 Jan 5;96(1):133-8.
14. Nama S, Awen BZ, Chandu BR, Kagga M. A novel validated RP-HPLC method development for the estimation of rimonabant hydrochloride in bulk and tablet dosage forms. African Journal of Pharmacy and Pharmacology. 2011 Feb 1;5(2):207-13.
15. Dalgleish R. The human type I collagen mutation database. Nucleic acids research. 1997 Jan 1;25(1):181-7.
16. Horwitz EM, Prockop DJ, Gordon PL, Koo WW, Fitzpatrick LA, Neel MD, McCarville ME, Orchard PJ, Pyeritz RE, Brenner MK. Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood, The Journal of the American Society of Hematology. 2001 Mar 1;97(5):1227-31.
17. Glorieux FH, Ward LM, Rauch F, Lalic L, Roughley PJ, Travers R. Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralization defect. Journal of Bone and Mineral Research. 2002 Jan 1;17(1):30-8.
18. KM K. Brittle IV mouse model for osteogenesis imperfect IV demonstrates postpubertal adaptations to improve whole bone strength. J Bone Miner Res. 2004;19:614-22.
19. Morello R, Bertin TK, Chen Y, Hicks J, Tonachini L, Monticone M, Castagnola P, Rauch F, Glorieux FH, Vranka J, Bächinger HP. CRTAP is required for prolyl 3-hydroxylation and mutations cause recessive osteogenesis imperfecta. Cell. 2006 Oct 20;127(2):291-304.
20. Ravella S, Angel M, Subramanian H, Thangavel N, Namballa M, Lokesh D, Mishra AK, Nagaraju GV. Navigating the Future of Cancer Diagnosis: A Comprehensive Review of Novel Approaches for Community-Based Treatment. future.;1:6.
21. Morgan JA, Marcus PS. Prenatal diagnosis and management of intrauterine fracture. Obstetrical & gynecological survey. 2010 Apr 1;65(4):249-59.
22. Viora E, Sciarrone A, Bastonero S, Errante G, Campogrande M, Botta G, Franceschini P. Increased nuchal translucency in the first trimester as a sign of osteogenesis imperfecta. American journal of medical genetics. 2002 May 15;109(4):336-7.
23. Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, Mortier G, Mundlos S, Nishimura G, Rimoin DL, Robertson S, Savarirayan R, Sillence D, Spranger J, Unger S, Zabel B, Superti-Furga A. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011 May;155A(5):943-68. doi: 10.1002/ajmg.a.33909. Epub 2011 Mar 15. PMID: 21438135; PMCID: PMC3166781.
24. Zhou X, Zhang Z, Feng JQ, Dusevich VM, Sinha K, Zhang H, Darnay BG, de Crombrugghe B. Multiple functions of Osterix are required for bone growth and homeostasis in postnatal mice. Proceedings of the National Academy of Sciences. 2010 Jul 20;107(29):12919-24.