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Review Article

Genetic Basis, Emerging Therapies and Research Perspectives in Osteogenesis Imperfecta

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ABSTRACT

Osteogenesis Imperfecta (OI) is a group of genetic skeletal disorders of connective tissues with fragile bones resulting in recurrent fractures. It can present in antenatal period, early childhood or adulthood, which caused by abnormal synthesis of collagen, abnormal bone matrix and weak bones. Multiple genes are implicated in pathohysiology and causation of OI. We describe here the different phenotypic features in OI, the genes and variants identified in various studies in children and adults, the management options available and the research done in osteoporosis including osteogenesis imperfecta.

Keywords: Bisphosphonates; Bone research; Fractures; lncRNAs; Osteoporosis; Variants

INTRODUCTION

Osteogenesis imperfecta can be autosomal dominant or autosomal recessive with most severe forms presenting antenatally with fractures and milder forms presenting in adolescence or adulthood. The overall incidence of genetic skeletal disorders at birth is variable in different geographic regions, and estimated to be 2.3 to 19.6 of 10,000 births. The prevalence of occurrence of OI is 1 in 15,000 to 20,000 births [1]. Fractures in the OI most commonly occur at age of childhood and a higher risk of fractures throughout the life. Bone Mineral Density (BMD) can be decreased in OI, emphasizing that lower bone quality due to flaws in the bone matrix and mineralization is a primary mechanism of bone fragility. The regulatory systems in intracellular and extracellular level are being decoded, along with the role of the Wnt-beta-catenin signaling mechanism in the regulation of various biological functions. In majority of cases this condition is caused by mutation in *COL1A1* or *COL1A2* genes that can lead to the abnormal production collagen. Mutations in *WNT1* genes are linked with OI type 15. Several other genes have also been recently identified in causation of autosomal recessive OI. Research on OI has been on developing new drugs for ameliorating the osteoporosis, improving bone strength and mobility and exploring role of lncRNAs in development of targeted therapies.

LITERATURE REVIEW

Phenotypes of OI

OI is a set of connective tissue illnesses characterized by bone fragility and a wide range of morphologies. Brittle bone disease or OI is an inherited bone disorder that is caused by the mutations in the several genes but most often due to mutations in the *COL1A1* or *COL1A2* genes that result in abnormal production of collagen tissue. OI affects roughly 1 in every 10,000 to 20,000 new born [1]. The nomenclature and classification of OI has evolved since 1780s. Several clinical observations, such as blue sclera of eyes, low bone mass, deafness/hearing impairment, fragility of bones, hypermobility, and joint hyper laxity, have been linked to OI over time. Dental anomalies have also been documented [2]. In the late 1970s, the development of molecular biology and radiological technologies allowed for the creation of an OI categorization based on clinical symptoms shown in Figure 1. There are different types of the OI, ranging from mild (type I) to deadly (type II). Types III and IV are severe kinds that allow survival beyond the new born period, but type V has a mild to moderate phenotype with interosseous membrane calcification. OI with blue sclera and dentinogenesis imperfecta are dominantly inherited in type I, whereas type II includes fatal perinatal OI with crumpled femora

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and beaded ribs on radiographs. The Sillence type III includes a gradually deforming OI while type IV comprises a dominantly inherited disorder with normal sclera.

Mutations in the collagen genes like *COL1A1* and *COL1A2* genes usually result in a decrease in the production of normal type-I collagen (col 1) or an increase in the synthesis of aberrant collagen. Although a defect in the collagen gene has been identified as the primary cause of OI for many years, a different mode of inheritance-autosomal dominant for OI types I and IV and autosomal recessive for OI types II and III—indicates genetic heterogeneity of the disease and the possibility that defects in other genes can cause OI. Traditional forms included congenita A, congenita B, and tarda A, and tarda B which accounted for 19 percent, 31 percent, 25 percent, and 25 percent in Shapiro's study [3]. Low bone density, increased bone instability, blue sclera of eyes, dental anomalies (normal enamel with defective dentin), and deafness/hearing loss are the most common clinical features of OI. Ligament laxity and greater joint mobility, as well as small height and easy bruising, are further characteristics. Though autosomal dominant OI is most common with age of presentation from childhood to adolescence; autosomal recessive forms have been identified with severe early presentation with antenatal and/or neonatal fractures, and bowing. The prognosis is poorer with earlier onset of the fractures. Figure 2 illustrates the X-ray findings in OI. During fracture healing, there is a possibility of hypertrophic callus (which might mimic osteosarcoma); although, most fractures heal at the normal rate. Protrusio acetabuli, proximal varus or anterolateral bending (femur), anterior bow (tibia), cubitus varus, and other proximal forearm deformities are known to occur as a result of recurrent fractures.

Genes implicated in OI

Individuals affected with OI can live a generally independent life, or they can have significantly handicapped with reduced mobility, using a wheelchair, and rely on caregiver support, depending on the severity of the condition and efficacy of therapies. Genes like *WNT1*, *COL1A1*, *COL1A2*, *CRTAP*, *IFITM5* are involved in causation of OI where there are recurrent fractures and bone deformities. Such genes and the proteins are involved in the regulation of development from fertilization to fully developed fetus, but due to pathogenic mutations; these gene products become non-functional and inhibit the process of development and cause many skeletal abnormalities including bone fractures and improper alignment of bones, abnormal remodeling of bones and cartilage. This leads to compromised mobility and premature death in affected children. Milder cases presenting in adolescence or adulthood have relatively better outcomes. There is macrocephaly in some patients with OI along with wormian bones. This has to be differentiated from abnormal skull in cleidocranial dysplasia [4]. Though majority (45-70%) of the cases have pathogenic variants in collagen genes, other gene mutations including *WNT1, TENT5A, SP7, MESD, FKBP1* etc. are also implicated. Several mechanisms are involved in the process of formation of bones and mineralization shown in Figure 3. Few of the protein encoding genes affect folding of collagen type I or post-translational changes such as *P3H1*, *CRTAP*, *PPIB* and *BMP1*. Following the literature [5-9], several disease-causing variants in the OI genes were identified. In Figure 4, most mutations are in *COL1A1* and *COL1A2* genes, also with significant contribution from *FKBP10*, *LEPRE1*, *SERFINF1* and *WNT1* genes.

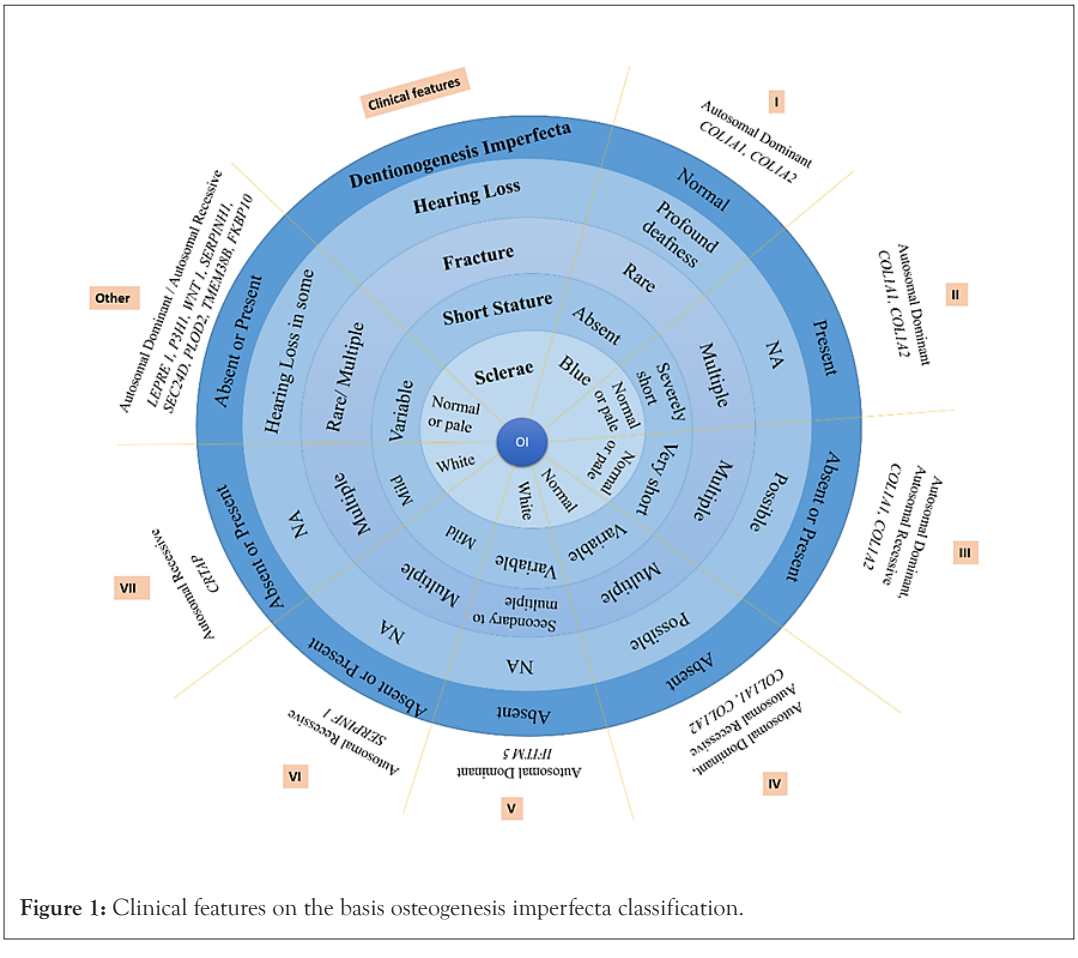

Figure 1: Clinical features on the basis osteogenesis imperfecta classification.

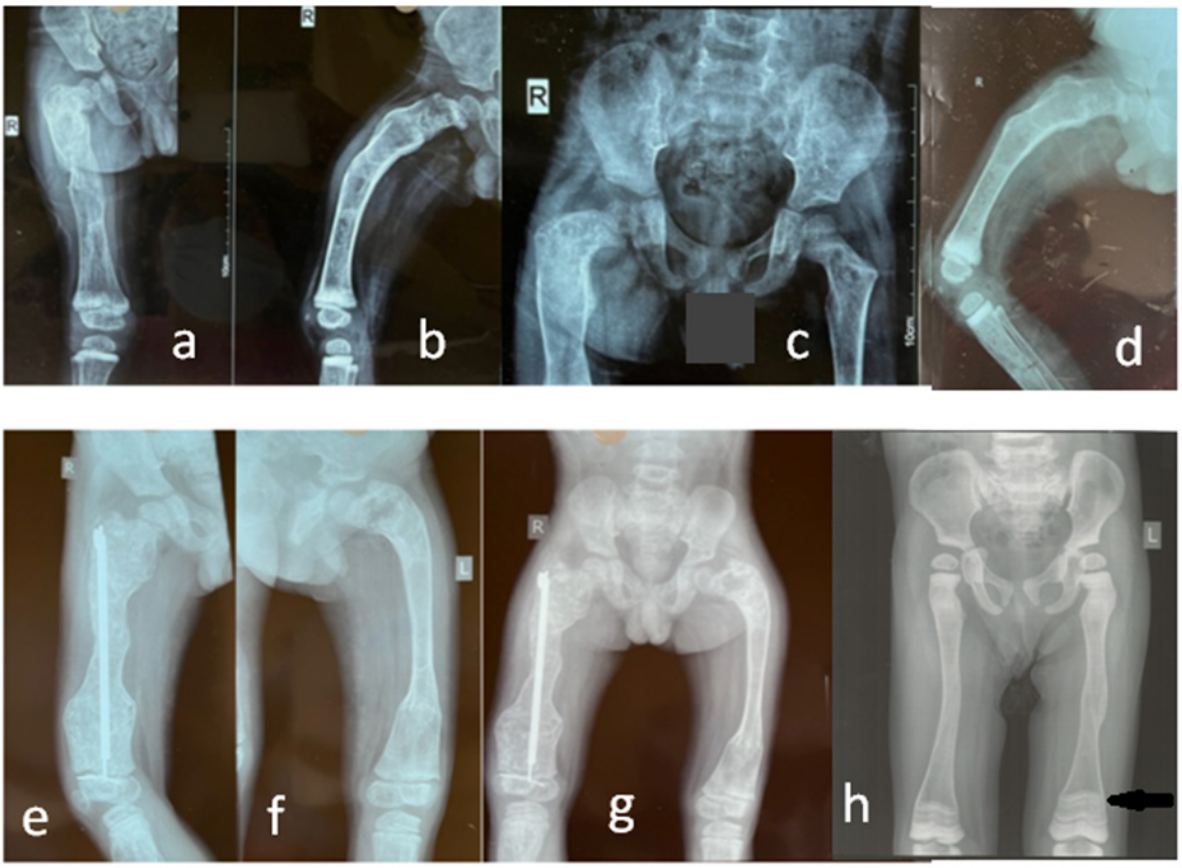

Figure 2: X-ray findings in children with severe osteogenesis imperfecta; showing osteopenia, shortening, bowing, and fractures before treatment (a,b,c,d); and abnormal remodeling, rod insertion, and zebra lines (arrow) after treatment (e,f,g,h).

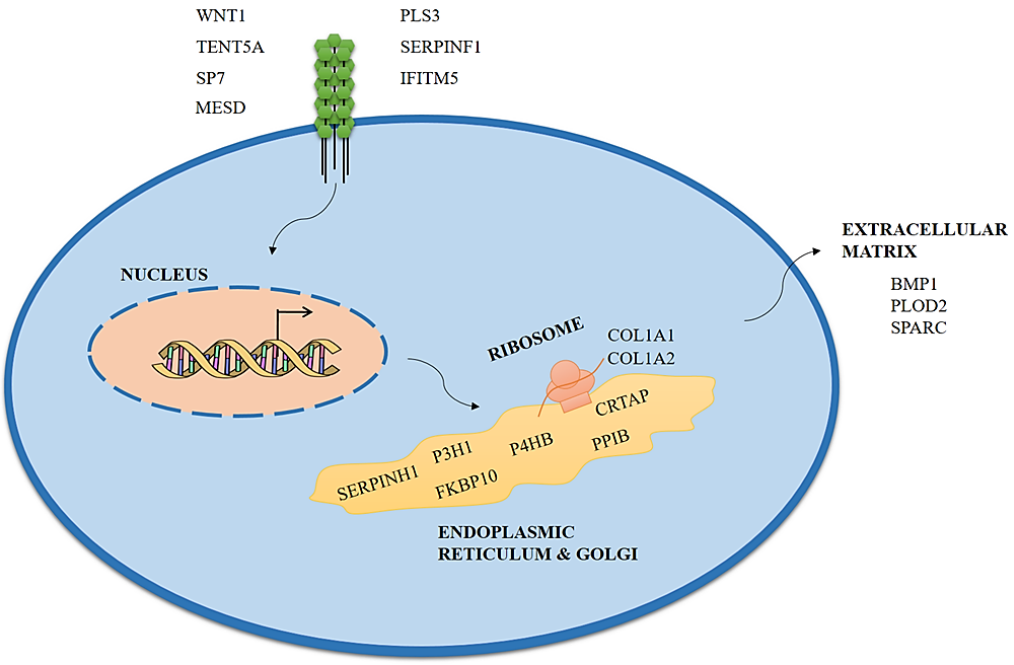

Figure 3: Pathophysiological mechanisms including long noncoding RNAs (lnc-RNAs) in osteogenesis imperfecta.

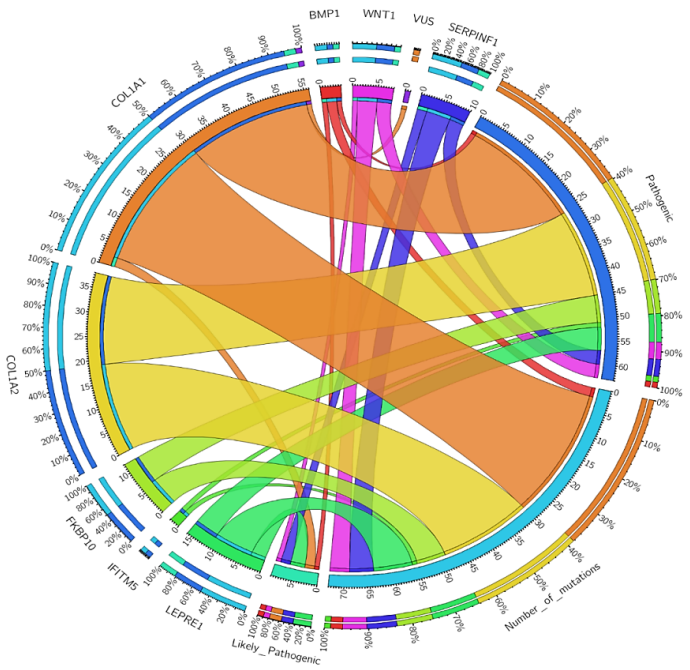

Figure 4: Circos plot of the molecular basis of osteogenesis imperfecta in Indian subcontinent. Most mutations are in *COL1A1* and *COL1A2* genes, also with significant contribution from *FKBP10*, *LEPRE1*, *SERFINF1* and *WNT1* genes. Of all pathogenic mutations, 40% are due to *COL1A1*, 30% due to *COL1A2*, 10 % due to *FKBP10*, 5-10% resulting from *LEPRE1*, *WNT1*, and *SERPINF1* (Made using CIRCOS software).

Of all pathogenic mutations, 40% are due to *COL1A1*, 30% due to *COL1A2*, 10 % due to *FKBP10*, 5-10% resulting from *LEPRE1*, *WNT1*, and *SERPINF1* as shown in Table 1. Genes such as SERPINH1 and *FKBP10* are involved in the intracellular trafficking and genes such as *MBTPS2* and *CREB3L1* are involved in the Endoplasmic Reticulum (ER) stress response and synthesis of protein. WNT canonical signaling pathway genes such as *WNT1* and *LRP5* play a role in the anabolic bone function and *WNT1* defect causes osteoporosis and OI and *LRP5* is linked to pseudo-glioma osteoporosis syndrome. Gene *Sp7* is essential for the osteoblast differentiation which is a zinc finger-containing transcription factor [10]. Long bone fractures and deformities due to defective mineralization characterize OI type VI, which is caused by loss of function mutations in *SERPINF1* (i.e., osteomalacia) [11]. Mutations in *BMP1* demonstrated varying effects on bone mass in human OI patients, but all cases reported frequent fractures associated with reduced cleavage of the collagen C-terminal domain [12]. Fractures in Bruck syndrome are caused by mutations in *FKBP10*, which are followed by a considerable reduction in telopeptide lysyl-hydroxylation and consequent inter-chain cross-linking [13]. In two separate families, a new missense mutation in *MPTBS2* disrupted a motif crucial for protease catalytic activity, resulting in a moderate/severe X-linked recessive form of OI [14]. In the same study, osteoblasts from OI patients had lower levels of *Creb3l1/OASIS* cleavage and LH1 levels, as well as lower levels of hydroxylation of helical lysine (K87) and a larger LP/HP ratio [14]. Major contribution to causation of OI is by *COL1A1* and *COL1A2* genes, up to 90% cases. Glycine substitutions in *COL1A1* and *COL1A2* account for over 40% of pathogenic mutations in the gene, and cause severe skeletal phenotype and short stature. Variants in *COL1A1* are 3 times more common than variants in *COL1A2*. However, other genes like *WNT1*, and *SERPINF1* account for most cases of autosomal recessive OI especially in patients from China but variants in *TMEM38B* were frequently seen in Palestinian population. In 48-70% of antenatal, neonatal and childhood onset OI, recessive genes are implicated especially in consanguineous families. Most of the variants are missense or frameshift (truncating) variants.

Table 1: Genes and their contribution to osteogenesis imperfecta in children and adults.

Genes	Number of pedigree (n/N)	% contribution	Variant type
COL1A1	4/94; 30/53	8.33; 69.8	Missense
COL1A2	3/94; 12/53	20.00; 27.9	Missense
WNT1	30/74	40.54	Missense/ frameshift
IFITM5	53/598; 1/53; 18/29	9; 2.3; 62.1	-
FKBP10	10/74	13.51	Nonsense/ frameshift/ splicing
SEC24D	3/74	4.05	Frameshift/ missense
TMEM38B	12/77	29	-
CRTAP	3/74; 17/598	4.05; 2.9	Nonsense/ frameshift
P3H1	3/74	4.05	Nonsense/ missense
P4HB	3/598	0.6	-
SERPINF1	22/74; 23/598	29.73; 4.00	Nonsense/ frameshift/ splicing

Emerging therapeutic options in OI

With more and more genes identified in causation of OI, the

phenotypes are being better characterized. However, the mainstay of therapy remains bisphosphonates [15,16]. There are different bisphosphonates used for therapy, of which pamidronate and zoledronate are given as IV infusion; and oral drugs include neridronate, ibandronate, risedronate, and alendronate among others. Zoledronate is a more potent bisphosphonate and found to be quite safe in children. *IFITM5*-related OI may not respond well to bisphosphonate therapy. Ibandronate given IV has also been tried in some adult bone disorders. However, combining bisphosphonates with denosumab- a RANK ligand antibody which has a role in inhibition of osteoclast maturation may be more beneficial in some patients with severe OI [17,18]. Monitoring includes serial evaluation of Bone Mineral Density (BMD) by DXA scan, skeletal MRI, and ratio of urinary dihydropyridinoline/creatinine.

Another monoclonal antibody-anti-sclerostin antibody or Romosozumab administration is helpful in treatment of osteoporosis-pseudoglioma syndrome caused by *LRP5* gene mutations [19,20]. Sclerostin (SOST) is an antagonist in the Wnt pathway, and decreases osteoblastogenesis. The source of SOST is primarily from the osteocytes. Romosozumab leads to increase in osteoblastogenesis and decrease in the bone resorption by uncoupling the remodeling in bone. It has been approved for severe osteoporosis treatment in several countries. In contrast, teriparatide administration is controversial in OI as a standalone drug as it increases SOST levels in Type I OI [21]. Anabolic treatment using Growth Hormone (GH) has also been tried to mitigate short stature in children with OI and Table 2 elucidates the approach to management in patients with OI.

Table 2: Approach to management of OI (OI); IV-Intravenous, Vit D-Vitamin D.

S.No.	Aim of therapy/ management	Approach
1	Reduce fractures	*Bisphosphonates IV/oral; safety precautions at home, avoid contact sports
2	Correction of deformities, improve mobility	Surgical intervention, insertion of intramedullary rods
3	Increase height gain in children	Growth hormone therapy- controlled use, with bisphosphonates
4	Normalize or improve hearing	Hearing aids, cochlear implants, other ear surgeries
5	Reduce kyphoscoliosis	Correct nutritional deficiencies with calcium, and vitamin D supplementation; maintenance of appropriate posture, use of corsets especially during travel
6	Improve cardiorespiratory function	Treatment of respiratory infections, appropriate ventilation strategies, guarded chest physiotherapy
7	Adjunctive therapies (unestablished yet)	Teriparatide, Denosumab, Romosozumab (anti sclerostin antibody)
8	Prevention in family	Mutation testing, genetic counselling, prenatal diagnosis in families with severe OI

Note: *Bisphosphonates may not be useful in *IFITM5*-related OI.

New areas of research in OI

Wnt-β-catenin signaling pathway has role in the development, formation, and patterning of the human skeleton and is elucidated by the several skeletal diseases (such as OI, osteoporosis) linked to the mutations in this signaling pathway. For example, loss of wnt3a leads to the congenital defect i.e., in which all the limbs was fail to form and other areas of the body also affected such as brain, pelvis, etc. [22]. *WNT1* gene mutations in heterozygous and homozygous state cause premature osteoporosis and OI respectively [8]. The loss-of-function alterations in the *LRP5* co-receptor is associated with the condition Osteoporosis Pseudoglioma (OPPG) syndrome and also linked to osteoporosis [23]. Whereas gain-of-function alterations of *LRP5* co-receptor leads to the enhanced bone strength and autosomal dominant high bone mass (opposite phenotype) [24,25]. Mutation in the Wnt-β-catenin signaling pathway gene: SOST, coding for sclerostin, an inhibitor of Wnt-β-catenin signaling; causes overlapping disease i.e., Sclerosteosis. It is a skeletal dysplasia that is caused by loss-of-function homozygous or compound heterozygous changes in the SOST gene, leads to the high bone mass and sclerotic bones.

Current studies have been shown important role for lncRNAs in several diseases including cancer, OI and related genetic disorders. There are many types of long non-coding RNAs, which can cause genetic disorders such as OI by interacting with a different types of genes and protein [26], eg., lncRNA WSPAR interacts with TCF complex regulate gene expression and translational protein modification which alter the protein function [27]. Several LncRNAs are involved in the wnt signaling pathway such as *MEG3, MALAT1, DANCR, NEAT1, NRON, WSPAR* and many more. H19 LncRNA regulates the differentiation of osteoblast through the mechanism including miR675/TGF-β/HDAC/smad3 pathway; as miR675 is present in the stating exon of the *H19* and miR675 targeting the degradation of the TGF-β due to the osteogenic effect of the LncRNA-*H19*; leads to the osteogenesis inhibition requires the activity of histone deacetylase [28]. Modulation of certain functional motifs in lncRNAs can help in therapy of osteoporosis. Recent studies in mice have identified that NRON negatively regulates the bone resorption and is a potential therapeutic target for reducing the bone resorption in OI and improving the bone mass [29].

DISCUSSION

OI affect bones right from fetal development, which persistently increased risk of fracture frequency. In majority of the cases, this condition is caused by mutation in *COL1A1* or *COL1A2* genes that can lead to the abnormal production collagen [9]. With an estimated, 40% are due to *COL1A1*, 30% due to *COL1A2*, 10 % due to *FKBP10*, 5-10% resulting from other causal recessive pathogenic variants in the other known genes or other as-of-yet-unknown genes. The management of OI involves administration of bisphosphonates and calcium and vitamin supplements [15,16,18]. Monitoring involves assessment of frequency of fractures and checking bone health with DXA scan, along with growth monitoring in children. Surgical management is needed especially for correction of deformities and malunion of fractured bone. Other treatment modalities need further validation with long term studies. Natural history would be variable in untreated cases depending on the cause of OI; and is expected to be fairly good in milder cases presenting in adolescents in adults with absence of spontaneous fractures. The aim of this write up was to emphasize

the state-of-art understanding the phenotypes, mutations in genes and research advances in OI. The role of lncRNAs appeared as an important players affecting bone formation and re-modeling and may be the possible biomarkers or therapeutic targets; also needed to be further validated. Also combination therapy with bisphosphonates and romosozumab or denosumab may be effective in selected cases but require further prospective studies in severe OI in children [17,20,21]. Role of growth hormone and timing of GH therapy also needs to be further analyzed in multicentric studies with homogenous patient population. Better biomarkers need to be developed for better monitoring in recessive or dominant OI. With availability of next generation sequencing, it is possible to identify causative variants in affected families [30]. Thus, appropriate genetic counseling can be done and preventive options for prenatal diagnosis or pre-implantation diagnosis can be discussed with the couples planning further pregnancies.

CONCLUSION

There have been rapid strides in understanding pathophysiology of rare inherited disorders and new therapies are being developed for OI including monoclonal antibodies and other translational agents. Technological advances in diagnosis and better therapy have improved outcomes in children with OI. The lncRNAs genetically and epigenetically control gene transcription and protein expressions and can be targets whose functional motifs can be modulated in therapy. Role of several genes in *Wnt* signaling pathways and lncRNAs, needs to be explored further in OI to enable development of effective therapies in management of severe bone disorders with osteoporosis.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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