

A Systematic Overview of Osteogenesis Imperfecta

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Abstract

Osteogenesis imperfecta (OI) is a heterogeneous rare connective tissue disorder commonly caused by mutations in the collagen type 1 gene. It is a worldwide extensive disorder regardless of age, gender or ethnic group for a children and adults. Typical clinical features are brittle bone, high frequency of fractures and bone deformities. The other observed signs are blue sclera, dentinogenesis imperfect and otosclerosis. In this review, author make a systematic overview, including the mechanisms, classification, diagnostic methods, related to human concerned disease and treatment. The review also focuses on the OI related so many health concern diseases. In OI patients maintaining of health is very important otherwise, the bone deformities and collagen defects common to OI it can affect various internal organs, leading to major or minor secondary problems. Individuals and optimization of OI treatment in children and adults remain a challenge, because available treatments do not target then underlying collagen defect. Treatment includes physiotherapy, surgical procedures and pharmacology therapy. In this brief review, author mainly discusses current knowledge of pharmacology therapies and possible future therapies for treatment of OI.

Keywords: Collagen type 1; Osteogenesis imperfecta; Bisphosphonates; Neridronate and teriparatide

Introduction

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bones that break easily, literally means “imperfectly formed bone”. People with OI have a genetic defect that impairs the body’s ability to make strong bones. It is also called as “brittle bone disease”. Severely affected patients have multiple fractures since childhood, both spontaneous and related to minimal trauma, and the most seriously affected children usually die in the neonatal period [1]. OI is a rare clinical disease, occurring at a rate of between 1/10,000 and 1/25,000 worldwide. Lack of a good understanding of difficulties in the diagnosis, optimal treatment, and recent progress about the disease in the world related to health concern this could potentially result in problems for physicians, such as missed diagnosis, diagnostic error, or litigation [2]. Hence, a systematic overview of the OI had been done in this review, in order to improve and understanding of this disease.

Molecular and clinical features

OI is a hereditary disease caused by a collagen defect, mostly caused by mutations of the genes coding the chains of collagen type 1 gene, which leads usually to autosomal dominant OI. Type I collagen is a rod-like structure formed from a trimer of 2 COL1A1 and 1 COL1A2 subunits, which requires post-translational modification. Many of the other rare forms of OI are due to defects in protein involved in cross-linking, hydroxylation, and mineralization of type 1 collagen [3]. Further molecular biology studies have found that the two chains have repeated Glycine-proline-hydroxyproline dextro-rotated triplet structures. The triplet structure is extremely important for the correct folding of the peptide chain. Abnormality in this triplet caused by genes changes, leads to incorrect alignment of the peptide and eventually to abnormal type 1 collagen [4].

Additionally, it is thought that cartilage-associated protein (CRTAP), prolyl 3-hydroxylase 1 (P3H1/LEPRE1) and cyclophilin B (CyPB/PPIB) also influence this triplet structure, and may be involved in the pathogenesis of OI. The major clinical manifestation is skeletal fragility. Skeletal deformity, joint laxity, and sclerosis may be present. Other extra skeletal manifestations include hearing loss, dentinogenesis imperfecta, blue/gray sclera, advancing deafness, beading of the ribs, hypercalciuria, aortic root dilatation, vascular, pulmonary complications and neurologic conditions such as macrocephaly, hydrocephalus, and basilar invagination [5]. The phenotype is variable, ranging from osteoporosis presenting in

adulthood to lethality in children. Even adults with “mild” OI may have significant musculoskeletal symptoms, including arthritis, fractures, back pain, scoliosis, and tendon ruptures [6].

Symptoms and signs

There are different types of OI with symptoms that range from mild to severe. Each person with the condition may have a different combination of symptoms. All people with OI, having weaker bones. Some common symptoms of OI includes: Short stature, Triangular-shaped face, breathing problems, hearing loss, brittle teeth, bone of deformities such as bowed legs of scoliosis [7]. There are several types of OI and they vary in severity and characteristics. As scientist have discovered new genetic problem causing OI, new types of the disorder have been recognized. All types of disorders and symptoms are described below.

Classification

Based on clinical signs, the first OI classification from David Sillence in 1979 [8]. This author divided the disease into four types (types I to IV). The majority of OI cases (possibly 85–90 percent) are caused by a dominant mutation in a gene coding for type 1 collagen. This classification has been used until recently; when four new types were added (types V to VIII) [9]. Table 1 summarizes the classification based on the involved genes from Type I to Type XV.

Type I, the mildest form of OI, multiple fractures, blue sclera, brittle teeth, and hearing loss. Fractures are common in neonatal period, but rare in the uterus or after adulthood have been reached. Type II is the most severe type, frequently causes death at birth or shortly after because of respiratory problems. Severe bone deformity, poor mineralization, beading of ribs, shortening of long bones, and multiple fractures.

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OI type	Inheritance	Affected Gene	Protein	Defect	Phenotype
Classical Silence types					
I	AD	COL1A1/COL1A2	$\alpha 1(1)$ collagen	Collagen quantity	Mild, non-deforming
II	AD	COL1A1/COL1A2	$\alpha 1(1)/\alpha 2(1)$ collagen	Collagen structure	Perinatal lethal
III	AD	COL1A1/COL1A2	$\alpha 1(1)/\alpha 2(1)$ collagen	Collagen structure	Progressive deformity
IV	AD	COL1A1/COL1A2	$\alpha 1(1)/\alpha 2(1)$ collagen	Collagen structure	Moderately deforming
V	AD	IFITM5	BRIL	Matrix mineralization	Moderate distinct histology, and hyperplastic callus
VI	AR	SERPINF1	PEDF		Moderate to severe
VII	AR	CRTAP	CRTAP	Prolyl 3 hydroxylation	Severe to lethal
VIII	AR	LEPRE1	P3H1	Prolyl 3 hydroxylation	Severe to lethal
IX	AR	PPIB	CyPB	Prolyl 3 hydroxylation	Moderate to lethal
X	AR	SERPINH1	HSP47	Collagen chaperoning	Severe
XI	AR	FKBP10	FKBP65	Telopeptide hydroxylation	Progressive deforming, Bruck syndrome
XII	AR	SP7	SP7/osterix	Osteoblast development	Moderate
XIII	AR	BMP1	BMP1/mTLD	Collagen processing	Severe, high bone mass
XIV	AR	TMEM38B	TRIC- B	Cation channel defect	Moderate to severe
XV	AR	WNT1	WNT1		Variable severity
	AD	WNT1	WNT1		Early- onset osteoporosis

AD=Autosomal Dominant, AR=Autosomal Recessive

Table 1: Classification of osteogenesis imperfecta types.

Type III is the most severe type in children's. Blue sclera are rare in this type, triangular face, scoliosis (abnormal curving of the spine) brittle teeth, possible hearing loss and often severe bone deformity. Type IV similar to type 1 but with mild to moderate bone deformity. Patients do not have blue sclera, large head, easy bruising and however shortening of the long bones is more obvious after adult hood has been reached.

Expanded classification

The molecular genetic classification of OI has shown to be very heterogeneous, with different patterns of inheritance and wide variability of clinical severity [10]. By studying the appearance of OI bone under the microscope, investigators noticed that some people who are clinically within type IV group had a distinct pattern to their bones. When they reviewed the full medical history of these peoples, they found the groups Type V and Type VI OI. The mutations causing these forms of OI have not been identified, but people in these two groups do not have mutations in the type 1 collagen genes.

Type V is a similar to Type IV OI in appearance and symptoms. Sclera is normal in colour. Unusually large calluses, called hypertrophic calluses, at the sites of fractures or surgical procedures. "Mesh- like" appearance to bone when viewed under the microscope. Only in 2012 were IFITM5 mutations identified in patients with type V OI, the gene encoding interferon γ -induced transmembrane protein 5, by sequencing of the entire exome [11].

Type VI, is an autosomal recessive form of the disease that can be caused by a homozygous mutation in the gene SERPINF1 in chromosome 17p13.3, causing a defect in mineralization of cartilage [12]. Distinctive "fish-scale" appearance to bone when viewed under the microscope.

After years of research, in 2006, scientists discovered two forms of OI that are inherited in a recessive manner. Genes that affect collagen formation cause both types. The discovery of these new forms of OI provides information for people who have severe or moderately severe OI but do not have a primary collagen mutation.

Type VII, results from recessive inheritance of a mutation in the CRTAP gene in homozygosity or compound heterozygosity in

chromosome 3p22. Partial expression of CRTAP leads to moderate bone dysplasia. Skeletal abnormalities and brittle bones. It accounts for 2% to 3% of cases of lethal OI [13].

Type VIII, severe growth deficiency and extreme skeletal under mineralization. It is caused by absence or severe deficiency of prolyl 3-hydroxylase activity due to mutations in the LEPRE 1 gene in a chromosome 1p34.2 associated with severe or lethal OI [14].

Type IX is an autosomal recessive form of OI corresponding to clinically severe types II/ III of the silence classification. It can be caused by a homogenous mutation in PPIB gene in chromosome 15q22.31 [15]. There are no reports of dentinogenesis imperfecta.

Type X is an autosomal recessive form of the disease that can be caused by a homozygous mutation in the gene SERPINH1 in chromosome 11q13.5. It is characterized by bone deformities and multiple fractures, generalized osteopenia, dentinogenesis imperfecta, and blue sclera [16]. Remaining types of mutation genes of OI type XI to type XV are mentioned in the Table 1.

Due to the high genetic complexity of the molecular basis of OI and the extreme phenotypic variability resulting from individual loci described in recent years. In 2009 the Nosology group of the International Society of Skeletal Dysplasias recommended maintaining the classification of Sillence as the prototypical and universally accepted form to classify the degree of OI severity, and freeing it from direct molecular reference [17]. Thus, as shown in Table 2, OI was grouped into five clinical categories, and the several genes that can cause OI were listed separately.

Diagnostic Methods

It is often possible to diagnose OI based solely on clinical features. Clinical geneticists can perform biochemical (collagen) or molecular (DNA) tests that can help confirm a diagnosis of OI in some situations. These tests generally require several weeks before results are known. Both the collagen biopsy test and the DNA test are thought to detect nearly 90 percent of all type 1 collagen mutations [18].

Routine prenatal screening by ultrasound or genetic testing can achieve good results for patients with positive family histories. However the detection rate is very low where there is no family history, which

Osteogenesis Imperfecta	Inheritance	Genes
Non deforming OI (type I)	AD X-linked	COL1A1/COL1A2 PLS3
Perinatal lethal (type II)	AD, AR	COL1A1/COL1A2, CRTAP, LEPRE1, PPIB, BMP1
Progressively deforming (type III)	AD, AR	COL1A1/COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERPINF1, WNT1
Moderate (type IV)	AD, AR	COL1A1/COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM38B
With calcification of the interosseous membrane and/or hypertrophic callus (type V)	AD	IFITM5

AD=Autosomal Dominant, AR=Autosomal Recessive

Table 2: Osteogenesis imperfecta classification according to the international society of skeletal dysplasias with addition of newly discovered genes.

can lead to missed diagnosis, diagnostic error, or litigation. Physicians should have a high index of suspicion for such cases.

Histomorphometry

In a small minority of cases the bone biopsy shows specific abnormalities, which help to establish the diagnosis of OI. The biopsies should be excellent quality and should be examined by observers who are thoughtfully familiar with OI [19].

Bone density measurement (BMD)

Although BMD is now widely available; few patients with OI have been investigated using this method. BMD is normal in tiny number of cases, even in the absence of degenerative spinal disease or hip abnormalities. In most cases, however, BMD is far below the normal range, as shown by the Z-score in children and T-score in adults. As in Osteoporosis, the low BMD is probably a major risk factor for further fractures. However, the definition of osteoporosis developed by the World Health Organization, i.e., a T-score lower than 2.5 have not been validated prospectively in adults with OI. Neither BMD measurement using ultrasound has been validated with OI [20].

Ultrasound

Being a non-invasive method, ultrasound is the main prenatal screening method. Most cases diagnosed prenatally by ultrasound are type II, with fewer case of type III. This is because types I and IV can be normal before birth, and types V to VIII are extremely rare in clinical practice [21]. Abnormalities found include reduced echoes, shortening of the bones, angulations, changes in curvature, multiple fractures and beading of the ribs. Discontinuity of bone can also cause a wrinkly appearance [22]. Transvaginal ultrasound can detect abnormality at the 14th week, whereas transabdominal ultrasound can detect abnormality only after 15th or 16th week [23]. This technique requires a highly experienced operator. In families with a prior abnormal child, this technique is reliable; otherwise it is easy to miss the diagnosis.

Calcium, phosphate and bone turnover marker

Serum calcium is normal in patients with OI. Hypercalciuria has been reported in some patients in the absence of prolonged immobilization, with no renal dysfunction or nephrocalcinosis. Serum 25-hydroxy-vitamin D is often low, indicating vitamin D deficiency secondary to lack of exposure to sunlight, which is fairly common in these patients [24].

Biochemical markers for bone turnover do not provide accurate information on bone structure in OI, although a selective decrease in serum levels of carboxy-terminal propeptide of type I collagen (PICP) has been reported. However, other bone turnover markers, such as osteocalcin, alkaline phosphatase and amino-terminal telopeptide of type I collagen are useful for monitoring children with OI [25,26].

Radiography of the uterus

Radiography of the uterus can be used when ultrasound and genetic testing have failed to diagnose strongly suspected cases. Besides the common changes of OI, this technique can detect the wormian bone, a single skull bone surrounded by sutures. When the number of wormian bones is greater than 10, this is considered to be a significant number of wormian bones (SNWB) and OI are highly likely [23]. Semler et al. used radiography on 195 OI cases (types I, III and IV). They found the incidence of SNWB in each type to be 35%, 96% and 78% respectively [27]. They declared that SNWB tends to appear in severe cases and can be a reliable tool for diagnosis. However this method can cause radiation injury. In addition, fetal movement and overlapping of fetal bones with the mother's bones can obscure the diagnosis [28].

Collagen analysis and genetic diagnosis

Skin biopsy used to be the main method of diagnosing OI. However this method took a long time (several weeks) and had poor accuracy. Wenstrup et al. analyzed 132 cases of OI and found the false negative rate was as high as 13.2%. Now, combined skin biopsy and DNA sequence testing are recommended to make the diagnosis. Some researchers have reported the use of chorionic biopsy under ultrasound guidance combined with DNA sequence testing for diagnosing OI. This method can make the diagnosis at the 14th week. However it is invasive and can cause injury to the infant or result in premature delivery [29]. The reliability of genetic testing has relied on the development of new techniques. Van Dijk et al. compared two techniques in 106 cases of mild OI. The first technique used electrophoresis of type I collagen protein combined with a COL1A1/2 gene sequence test. The latter used multiplex ligation-dependent probe amplification (MLPA). They found that MLPA was the superior and more reliable method for finding genetic abnormalities [30].

OI related to health concern diseases

In OI patients maintaining of health is very important otherwise, the bone deformities and collagen defects common to OI it can affect various internal organs, leading to major or minor secondary problems. These include:

Lung problems

People with OI are more vulnerable to lung problems, including asthma and pneumonia. Viral and bacterial infections can become severe. Lung problems result from a combination of factors. If the ribs and spine do not develop normally, there is a less space for the lungs to expand. Collagen also is an important building block of connective tissue in the lungs. Decreased chest volume, chronic bronchitis, and asthma can lead to restrictive pulmonary disorder. This makes it difficult for people with OI to get enough oxygen through their bodies. In addition, they may have problems coughing effectively to clear away mucus [31]. In fact, respiratory failure is the most common cause of death in people with OI. In such cases, delayed extubation is necessary,

bronchodilators, antibiotics and inhaled corticosteroids can reduce local edema [32].

Cardiac problems

A small number of adults with OI seem to have heart valve problems. The most common is called mitral valve prolapsed. Shokoufeh et al., have reported that coronary artery aneurysm is a rare cardiac complication in OI [33]. 85 percent of heart muscle consists of type I collagen and OI before patients tend to also have congenital heart disease. The fragility of the cardiovascular structure results in a lower tolerance for surgery. It is therefore necessary to assess such patients carefully before surgery [34]. High cholesterol and related lipid disorders that may occur in families can contribute to heart problem as well. Medical management of these disorders includes appropriate diet, drug therapies, and regular monitoring by primary care doctor. Along with diet, drugs such as statins can be helpful in controlling lipids.

Neurological problems

People with OI often have enlarged heads, called macrocephaly. They can also have a condition called hydrocephalus, in which fluid builds up inside the skull, causing the brain to swell. People with severe OI often basilar invagination, a malformation of the spinal column that puts pressure on the spinal cord and brain stem. It causes severe headache, changes in facial sensation, lack of control over muscle movements, and difficulty swallowing. If untreated, basilar invagination can lead to rapid neurological decline and inability to breathe [35,36].

Abnormal blood coagulation

Edge et al, have reported that OI cases have increased vascular fragility, reduced clotting factors VIII and abnormal platelet function [32]. It is necessary to regular check coagulation function and platelet counts. Even in cases with normal coagulation, post-operative bleeding is possible. Blood transfusion is needed because fresh blood containing all of the clotting factors is the best choice [34].

Thalassemia

Osteopenia and osteoporosis are important cause of morbidity in patients with β -thalassemia major. In the pathogenesis of thalassemia-induced osteoporosis, genetic and acquired factors have been recognized [37]. Notwithstanding optimal therapeutic regimens, effective iron chelation therapy and adequate hormone replacement, unbalanced bone turnover and active bone resorption remain a major issue. The increased bone turnover rate observed in the thalassemic patients justifies the use of powerful antiresorptive drugs, such as bisphosphonates [38].

Periodontitis

Periodontitis is a multifactorial chronic infectious disease characterized by a loss of the connective tissue attachment to the teeth and the resorption of the alveolar bone due to the inflammatory processes. The etiology of periodontal disease is reducible to bacterial infection, which results in an inflammatory reaction. Tissue damage is generated by collagenolytic enzymes such as matrix metalloproteinase's (MMPs) which significantly contribute to periodontal tissue damage. Therapies aimed to blocking tissue damage mediated by MMPs and at blocking alveolar bone destruction are actively being sought by bisphosphonates [39].

Gastric function

Gastric problems are not uncommon in OI. These include gastric acid flux, which is aggravated by a decrease length of the chest cavity,

and chronic constipation. Small stature and frequent use of various pain medications can contribute to the problem.

Kidney stones

There appears to be a risk of kidney stones in about 20 percent of people who have OI. These may be caused by the increased calcium intake that results from changes in medications or diet. To see if calcium levels are too high, the doctor may recommend that a change in medications or diet be followed by a 24-hour urine calcium excretion evaluation [40].

Basilar impression (BI)

Also known as basilar invagination, BI is a special problem for adults with type III and IV OI. It involves pressure from the spinal column on the base of the skull. Symptoms of BI can include headache, muscle weakness, and tingling or numbness of hands and feet. Evaluation by a neurologist, examining of an MRI of the cervical spine and base of the skull, is necessary [41].

Hearing

Approximately 50 percent of all adults with OI will experience some degree of hearing loss during their life time. Hearing tests and MRI of the hearing canals can help your doctor understand the involvement of the bones in the ear. Treatment for hearing loss usually begins with hearing aids. Some adults are candidates for their stapedectomy or cochlear implant surgery [42].

Vision

The connective tissue problem in OI can extend to the eyes. Eyes exams are recommended every 2 to 3 years. OI can affect the shape of the lens and the strength of the sclera. So for this reason, adults with OI should consult the ophthalmologist before using contact lenses. Also, laser surgery is not recommended for people with OI [43].

Delayed wound healing

Abnormal type 1 collagen in OI cases makes them prone to delayed wound healing or disunion [2].

Bone mass and bone deformity

Low bone mass is a clinical characteristic of OI and individuals with this disorder tend to have markedly reduced areal bone mineral density (BMD). This reduced bone can be consequence of decreased bone size or decreased volumetric BMD or both [44]. Studies of iliac crest biopsies have revealed lower bone tissue quantity in children with moderate and severe OI, including reduced bone volume fraction, and decreased trabecular and cortical thickness. Decreased bone volume, through less marked, was also noted in some children with mild OI [45,46].

In addition to decreased bone mass and reduced bone material quality (low bone material strength), deformities of the spine and long bones are common in OI. For example, children with severe OI often exhibit anterolateral bowing of the femur and anterior bowing of the tibia [47]. Increased curvature in long bones leads to an increase in maximum stresses within the bone shaft. The increased stresses attributed to bone deformities in OI can further contribute to the risk of bone fracture [48].

Current knowledge of OI treatment

An important part of managing OI and staying healthy is assembling a good health care team and having a solid working relationship with

primary care doctor and medical specialists. The medical team may include an orthopedic, endocrinologist, pulmonologist, neurologist, surgeon, radiologist and nutritionist etc. There is not yet a cure for OI. Treatment is individualized and depends on the severity of the disease and the age of the patient. Treatment is directed towards preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Care of fractures, extensive surgical and dental procedures and physical therapy are often recommended for people with OI. Use of wheel chairs, braces and other mobility aids is common, particularly among people with more severe type of OI [18].

Physical therapy

The goals of the treatment in OI are to decrease pain and fractures and to maximize mobility. Physical therapy/ rehabilitation are particularly important in children to improve weight bearing and prevent fractures as well as to increase strength and mobility during fracture recovery. A physical rehabilitation program can include strengthening of deltoids, biceps and important lower muscles, such as gluteus maximus, gluteus medius, and trunk extensors. Some children may require wheelchairs or walking aids. Occupational therapy may be needed to help with daily living activities [1].

Surgical treatment

Some people with OI undergo surgery to correct bone deformities, including scoliosis and basilar invagination. A common surgical procedure for OI patients, "rodding" is the placement of metal rods in the long bones of the legs. This strengthens them and helps prevent fractures. Surgical treatment is mainly performed to correct deformities and to reduce the bone brittleness as the result of bad bowing and to improve the physical condition of the individual. Surgical intervention is also one of the possible solutions of otosclerosis in which the patient undergo stapedectomy (surgical removal of the stapes) [49].

Saldanha et al. applied external fixation to correct the abnormality in six OI cases and achieved good results [50]. Additionally, Agarwal and Joseph followed 44 special OI cases with repeated fractures between 1989 to 2003. Nine non unions were encountered in eight patients. They therefore considered that non-union was common in OI cases [51]. That's why care should be taken to choose correct fixation with fractures and surgical treatments. Surgery can restore the shape of long bone, but the functional recovery is limited because of abnormalities in the surrounding soft tissue. Surgery can also be performed to improve hearing loss. Patients are also advised to perform light physical activity (swimming, walking in water, Nordic walking) to strengthen the weakened muscles.

Pharmacologic therapy

Scientists are exploring several medications and other treatments for their potential use to treat OI. These include growth hormone treatment, intravenous and oral drugs called bisphosphonates, an injected drug called teriparatide (for adults only) and gene therapies. It is not clear whether people with recessive OI and those with dominant OI will respond to these treatments in the same manner.

Bisphosphonates

In current practice, several kinds of bisphosphonates are used to treat OI. Bisphosphonates (BPs) are non-hydrolysable synthetic analogs of pyrophosphate. BPs is a drug used to treat osteoporosis. They also are useful for OI, especially in children. These drugs do not built new bone, but they slow the loss of existing bone. They have been shown

to reduce vertebral compressions and some long bone fractures [52]. Intravenous BPs is currently the primary treatment of children with moderate to severe OI. BPs increase BMD and size in children with OI. BPs does not appear to impair bone formation that increases cortical within children with OI [53]. Observational studies suggest decreased fracture, decreased bone pain, and improved vertebral shape. Ability to perform activities of daily living may also be improved. However, it has been difficult to confirm all of these benefits in randomized trials, and the optimal duration of BP treatment is unknown [3,54]. David Gatti et.al revealed that BPs had been used for a standard therapy of bone disease related to malignancy. In breast cancer patients with bone metastasis, several BPs demonstrated clinical efficacy [55]. Zoledronic acid was the most extensively studied bisphosphonate in patients with bone metastases from prostate cancer or other solid tumors, and it remains the only bisphosphonate registered worldwide for these indications. In multiple myeloma, bisphosphonate treatment reduces the risk of pathological vertebral fractures, skeletal-related morbidity and pain [56,57]. In a recent case study, 11 years follow up of a man with OI type 1 who was treated with combined bisphosphonates and alfacalcidol is more effective in increasing BMD or preventing fractures than single treatment with bisphosphonates alone. This combined treatment is also very useful in postmenopausal women with OI [58]. The BPs most often used is ibandronate, alfacalcidol, pamidronate and zoledronate.

In a study of children with predominantly mild OI, oral risedronate increased BMD and appeared to decrease clinical fractures. Atypical fractures have been reported in children with OI treated with BPs; however, osteonecrosis of the jaw does not appear to be a major problem in children with OI treated with BPs [59,60]. Several studies have been done on the use of intravenous or oral BPs in adults with OI. Although BMD increases have been reported during these treatments, fracture data are equivocal [61]. A Cochrane review found increased BMD in patients with OI treated with BPs but did not find definitive evidence of fracture reduction. Furthermore, a recent meta-analysis of placebo controlled trials suggested that the effects of BPs for fracture prevention in OI were inconclusive [62,63].

Neridronate

Findings of a recent study are shedding new light on neridronate (6-amino-1-hydroxy-hexylidene-1, 1-bisphosphonate), an aminobisphosphonate widely used in the treatment of bone diseases and with specific therapeutic indications for OI and Paget's disease of bone (PDB) in Italy. A clinical study of David Gatti et al revealed, that a characteristic property of neridronate is that it can be administered both intravenously and intramuscularly, providing a useful system for administration in home care for a OI and PDB [55]. Treatment with BPs, in particularly oral treatment with pamidronate, was first reported on a 12-year old child in 1987 by Devogelaer et al. [64] Since then, BPs (generally pamidronate) administered intravenously have become the common treatment in children, with clinical evidence of significant increases in bone mineral density (BMD) and decreases in fracture incidence. A study of pamidronate in OI has reported a reduction of as much as 70% in bone growth rate at the end of a 5.5 year follow up [65].

Neridronate has been extensively investigated in patients with OI. In growing children, the neridronate treatment induces a rapid increase in BMD and a significant 64% decrease in fracture numbers, and similar results have been obtained also in newborns (<12 months old) affected by the more severe forms of the disease, with some evidence of improvement in the rate of skeletal growth. The treatment has also been tested in adults with OI, with evidence of efficacy in lowering fracture rate [66].

Pamidronate and neridronate proved equally efficient in improving vertebral area and vertebral indices of patients with OI. The huge benefit in treating patients with neridronate instead of pamidronate is the reduced time of hospitalization [55]. This is extremely important for the patients and their families and should lead to an increased quality of life in these severely handicapped children.

Estrogen

Some other researchers have proposed that estrogen can be used to treat infant OI. Antoniazzi et al. reported the effect of estrogen and neridronate on 30 children with OI [67]. They found that the combination of these two drugs produced superior results (in regard to bone content, growth rate, and fracture rate) compared with treatment with bisphosphonates alone in the children's pretreatment condition. Multiple drug combination therapy is a prospective direction for OI treatment. However, only few studies have been performed treating OI patients with growth hormone.

Growth hormone (GH)

Growth hormone has anabolic effects on bone. A study has conducted, randomized controlled clinical trial evaluating the effects of a combined treatment of neridronate and GH in children with mild and moderate OI [68]. Some studies explain that whether the combination of neridronate and GH can further improve the bone metabolism of children with OI who are already receiving treatment with neridronate. The effect of the combination drug was encouraging, as BMD at the lumbar spine and wrist as well as in the lumbar spine protected area increased significantly [55]. Some authors reported that the combination of recombinant GH and bisphosphonates is still under investigation and may be beneficial for OI types I, III and IV to increase linear growth, although these patients are not endogenously GH deficient [67].

Teriparatide

Teriparatide (PTH1-34) is an anabolic agent that stimulates bone formation (and ultimately bone resorption). This drug decreases vertebral and non-vertebral fractures in post-menopausal women with osteoporosis [69]. Recently a randomized trial of teriparatide in adults with OI showed increased BMD as well as increased vertebral strength estimated by FE analysis [70]. The benefit occurred only in mild OI not in severe OI. Observational studies have shown a positive effect on BMD in postmenopausal women with a statistically significant 3.5% increase in lumbar spine BMD [71]. Further studies are needed to clarify whether treatment with teriparatide is superior to treatment with bisphosphonates or other anti-resorptives in adult patients with different types of OI. Teriparatide is not an appropriate drug for children due to the risk of bone Cancer.

Denosumab

Denosumab is a monoclonal to receptor activator of nuclear kappa B ligand that decreases bone resorption, increases bone density, and reduces fractures in women with postmenopausal osteoporosis and also reduce the risk of bone-related events in patients with cancer that has spread to the bone [72]. This drug may represent a future therapy in OI. In a Hoyer-Kuhn study, four children with type IV OI, increased BMD and mobility and improved vertebral shape were reported after denosumab treatment and outcome of this study indicated that this treatment is safe [73]. There is also another report of denosumab treatment use in two children's with OI caused by COL1A1/A2 mutations. Denosumab has been reported to cause hypophosphatemia, hypocalcemia, and secondary hyperparathyroidism in a child with fibrous dysplasia of bone [74].

Cell-based therapy

Recently cell therapy and gene therapies are current issue in the treatment of this disease. The essence of cell therapy is the transplantations of bone marrow matched donors. OI patients who have undergone a cell therapy show an increase in a bone mineral content and an increase in body weight. Parental somatic mosaicism is thought to underlie about 50% of classical OI, and the observation that these mosaic parents are phenotypically normal has provided rationale for different cell-based therapies [7]. Along these lines, bone marrow transplantation has been carried out in OI patients in clinical trials, aiming at introducing normal osteoblasts through differentiation of mesenchymal stem cells. A few positive reports have been published, despite low numbers of engrafted cells [75]. Induced pluripotent cells could be another possible option; these could potentially be engineered to produce any desired tissue, including bone-forming cells for OI patients. This approach has been studied *in vitro* in mesenchymal cells from OI patients [76].

Gene therapy

The aim of a gene therapy is to prevent expression of mutant alleles. This is achieved by binding of complementary antisense DNA / RNA fragments or hammerhead ribozymes to abnormal pre-mRNA. A gene therapy using these mechanisms results in the conversion of severe type of OI in mild forms of the disease. For severe dominant OI, a therapeutic vision is silencing the mutated allele by gene therapy, i.e. allele-specific silencing. For a COL1A1 mutation, the consequence would be COL1A1 haplo-insufficiency, thus converting a severe phenotype to mild OI (similar to type 1). Heterozygous COL1A1 null alleles have no overt phenotype. There are several publications that report successful allele-specific gene silencing using siRNAs discriminating single-nucleotide variants with specific mRNAs [77,78]. A recent publication has reported that allele-specific silencing of COL1A1 using short hairpin RNAs reduced the amount of mutant collagen in *Brl/ + mice*, a murine model for classical dominant OI. Another approach in a gene therapy can be modification of mesenchymal stem cells of OI patients *in vitro* and consequent returning of these cells to the individuals [79].

Stem cell transplantation

Stem cell transplantation is a newly developed approach for the management of OI. Transplantation of mesenchymal stem cells (MSC) has the potential improve the bone structure, growth and fracture healing. Jerry et al. [80] summarized, the two patients with OI who have received pre and postnatal transportation of MSC. Some author suggests that prenatal transportation of allogeneic MSC in OI is safe. The cell therapy is of likely clinical benefit with improved linear growth, mobility, and reduced fracture incidence. Horwitz et al [81], reported bone marrow transplantation or bone marrow derived stem cells for OI patients. They found these methods achieved good clinical results even when in low concentrations. Li et al [82] transplanted mouse bone marrow mesenchymal stem cells into the femoral cavities of OI mice. Those exogenous mesenchymal stem cells changed into osteoblast cells in the OI mice and improved bone growth. Vanleene et al. transplanted human fetal blood stem cells into OI fetal rats in the uterus. They also found these stem cells changed into osteoblasts, secreting osteocalcin and synthesizing type I collagen. He observed that beneficial effect of human fetal blood stem cells or other stem cells will have a bright future in the human fetus with OI [83]. Thus it is appropriate to use stem transplantation in OI treatment.

Potential Future therapies for OI

Receptor activator of nuclear factor kappa-B ligand (RANKL),

also known as tumor necrosis factor ligand super family member 11 (TNFSF11). The future of OI treatment also continues to look promising. Bargman and her colleagues presently conducting animal studies of a new class of drugs known as RANKL inhibitors. "Instead of rendering osteoclasts less effective, these drugs interfere with the formation of osteoclasts" [84]. Sclerostin is an inhibitor of the LRP5/Wnt system that decreases bone formation. Some preclinical studies observed that sclerostin monoclonal antibodies have demonstrated a robust osteoanabolic effect with increases in bone formation, bone mass and strength in OI. Sclerostin antibody appeared to be effective in a mouse model of moderately severe OI, but less in a mouse model of more severe OI [85,86].

Excessive transforming growth factor beta (TGF β) signaling is an important mechanism of OI in both recessive and dominant OI mouse models. TGF β is secreted by osteoblasts and increases osteoblastic bone resorption. Anti TGF β therapy and Gene therapy with allele-specific silencing may represent as interesting prospect for the future treatment of OI [87].

Future perspectives

Larger study cohorts are needed to properly investigate the efficacy of pharmacological intervention, and efforts are underway to have national and international OI registries to make this possible. Such registries/cohorts could also be the basis for future research into genotype vs phenotype for prediction of disease severity and pharmacogenetic studies on the choice of medical treatment based on the patient's mutation.

Conclusion

Osteogenesis imperfecta is a heterogeneous disorder with a wide spectrum of clinical characters and a large genetic diversity. Although most cases of OI are caused by COL1A1/ A2 mutations, many new genetic causes have been identified in recent years. Some of these genes are related to the processing of type 1 collagen. In the present study, author makes a systematic overview of OI with clinical features, classification and diagnosis. The review also focuses on the OI related so many health concern diseases. In OI patients maintaining of health is very important otherwise, the bone deformities and collagen defects common to OI it can affect various internal organs, leading to major or minor secondary problems. There is not yet a cure for OI, still treatment is directed towards preventing or controlling the symptoms vary from person to person. The author of the current article has reviewed several treatments, BPs is the most widely investigated and used treatment for moderate to severe OI. Some of the benefits seen in observational studies have been hard to prove in controlled studies. Neridronate has been extensively investigated in patients with OI. In growing children, the neridronate treatment induces a rapid increase in BMD. A recently published study of the effects of teriparatide in adult OI has shown positive effects on BMD, atleast in mild disease. BPs and teriparatide appear to increase in BMD, but fracture data are lacking. Recent trials investigate that teriparatide appears to increase bone strength as estimated by FE analysis in adults with mild OI. Gene therapy may be a possible future treatment option for severe OI. Still scientists are investigating a promising treatment for OI.

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