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 1 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), proly 13- hydroxylase 1 (P3H1/LEPRE1) and cyclophilin B (CyPB/ PP1B) 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, hypercalcicuria, aortic root dilation, 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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Type III is the most severe type in children. Blue sclera are rare in this type, triangular face, scoliosis (abnormal curling of the spine) brittle teeth, possible hearing loss and often severe bone deformity. Type IV similar to type I 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 –induced transmembrane protein 5, by sequencing 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 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 LEPRE1 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 PPP1B 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 SERPHN1 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 Silence 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% 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
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. Hypercalcemia 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 1 collagen (PICP) has been reported. However, other bone turnover markers, such as osteocalcin, alkaline phosphatase and amino-terminal telopeptide of type 1 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 OI related to health concern diseases [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 prolapse. 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

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 [42].

Delayed would healing

Abnormal type 1 collagen in OI cases makes them prone to delayed 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 stylus) [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 zoledonate.

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 is 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 particular 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 COLIA1/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 COLIA1 mutation, the consequence would be COLIA1 haplo-insufficiency, thus converting a severe phenotype to mild OI (similar to type 1). Heterozygous COLIA1 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 COLIA1 using short hairpin RNAs reduced the amount of mutant collagen in Brlt/+ 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 transplantation 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. Vanleeene 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 LR5p/ 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 (TGFβ) signaling is an important mechanism of OI in both recessive and dominant OI mouse models. TGFβ is secreted by osteoblasts and increases osteoblastic bone resorption. Anti TGFβ therapy and Gene therapy with allele- specific silencing may represents 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 COLA1/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. Neronidone has been extensively investigated in patients with OI. In growing children, the neronidone 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, albeit 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.

References

1. Rauch F, Glorieux FH (2004) Osteogenesis imperfecta. Lancet 363: 1377-1385.
2. Zhao X, Yan SG (2011) Recent progress in osteogenesis imperfecta. Orthop Surg 3: 127-130.
3. Joseph L S, Carolynne A, Jessica F, Gerald H (2015) Recent development in Osteogenesis Imperfecta [v1; ref status: indexed, http://f1000.
4. Gerhard DS, Wagner L, Feingold EA, Shennem CM, Grouse LH, et al. (2004) The status, quality, and expansion of the NIH full-length cDNA project: the Mammalian Gene Collection (MGC). Genome Res 14: 2121-2127.
5. Biggin M, Munns CF (2014) Osteogenesis imperfecta: diagnosis and treatment. Curr Osteoporos Rep 12: 279-288.
6. McKiernan FE (2005) Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. Osteoporos Int 16: 1698-1702.
7. Lucie S, Ivan M (2011) Osteogenesis imperfecta Type I-IV, the population disorder of connective tissue in Czech population. EBII 7: 59—64.
8. Silence DO, Senn A, Dankis DM (1979) Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16: 101-116.
9. Starr SR, Roberts TT, Fischer PR (2010) Osteogenesis imperfecta: primary care. Pediatr Rev 31: e54-64.
10. Marini JC, Blissett AR (2015) New genes in bone development: what’s new in osteogenesis imperfecta. J Clin Endocrinol Metab 98: 3095-3103.
11. Cho TJ, Lee KE, Lee SK, Song SJ, Kim KJ, et al. (2012) A single recurrent mutation in the 5'-UTR of IFITMS causes osteogenesis imperfecta type V. Am J Hum Genet 91: 343-348.
12. Balasubramanian M, Parker MJ, Dalton A, Giunta C, Lindert U, et al. (2013) Genotype-phenotype study in type V osteogenesis imperfecta. Clin Dysmorphol 22: 93-101.
13. Barnes AM, Chang W, Morello R, Cabral WA, Weiss M, et al. (2006) Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. N Engl J Med 355: 2757-2764.
14. Cabral WA, Chang W, Barnes AM, Weiss M, Scott MA et al (2007) Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/ severe osteogenesis imperfecta. Nature Genet 39: 359—365.
15. van Dijk FS, Nesbitt IM, Zwikstra EH, Nikkels PG, Piersma SR, et al. (2009) PPIB mutations cause severe osteogenesis imperfecta. Am J Hum Genet 85: 521-527.
16. Christiansen HE, Schwarz U, Pyott SM, AlSwaid A, Al Balwi M et al (2010) Homozygosity for a missense mutation in SERPINH1, which encodes the collagen-chaperone protein HSP47, results in severe osteogenesis imperfecta. Am J Hum Genet 86: 389—398.
17. Eugenia RV, Tulla BC, Paula MS, Ana CO, Bernhard Z (2014) What is new in genetics and osteogenesis imperfecta classification? J Pediatr (Rio J) 90: 534—541.
18. National institute of health: Osteoporosis and related bone diseases (2012) Osteogenesis Imperfecta Overview. www.bones.nih.gov.
19. Glorieux F, Bishop N, Travers R, Roughely P, Chabot G et al (1997) Homozygosity for a missense mutation in SERPINH1, which encodes the collagen-chaperone protein HSP47, results in severe osteogenesis imperfecta. J Bone Miner Res 12: 389—399.
20. Zions LE, Nash JP, Rude R, Ross T, Stott NS (1995) Bone mineral density in children with mild osteogenesis imperfecta. J Bone Joint Surg Br 77: 143-147.
21. Bulas D, Stern HJ, Rosenbaum KN, Fonda JA, Glass RB, et al. (1994) Variable prenatal appearance of osteogenesis imperfecta. J Ultrasound Med 13: 419-427.
22. Thompson EM (1993) Non-invasive prenatal diagnosis of osteogenesis imperfecta. Am J Hum Genet 45: 201-206.
23. Abtin DS (1998) Osteogenesis imperfecta: a review. Can Assoc Radiol J 49: 110-123.
24. Chines A, Boniface A, McAllister W, Whyte M (1995) Hypercalcitria in osteogenesis imperfecta: a follow-up study to assess renal effects. Bone 18: 333-339.
25. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, et al. (1998) Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 339: 947-952.
26. Shapiro JR, Copley C, Goldsborough D, Gelman R and Barnhart K (1995) Effect of pamidronate on bone turnover and IGF- I in type 1 Osteogenesis Imperfecta. J Bone Min Res 10: 604.
27. Semler O, Cheung MS, Glorieux FH, Rauch F (2010) Wornian bones in
osteogenesis imperfecta: Correlation to clinical findings and genotype. Am J Med Genet A 152A: 1681-1687.
28. Ghosh A, Woo JS, Wan CW, Wong VC (1984) Simple ultrasonic diagnosis of osteogenesis imperfecta type II in early second trimester. Prenat Diagn 4: 235-240.
29. Wenstrup RJ, Willeing MC, Slarman BJ, et al (1990) Distinct biochemical phenotypes predict clinical severity in nonlethal variants of Osteogenesis Imperfecta. Am J Hum Genet 46: 975-982.
30. van Dijk FS, Huizer M, Kariminejad A, Marcelis CL, Plomp AS, et al. (2010) Complete COL1A1 allele deletions in osteogenesis imperfecta. See comment in PubMed Commons below Genet Med 12: 736-741.
31. Osteogenesis Imperfecta Foundation 2008 (2012) Respiratory issues in Osteogenesis Imperfecta. Retrieved May 7, from www.of.org/site/ Docserver/Respiratory_issues. docID=7621.
32. Edge G, Okato B, Fennelly ME, Ransford AO (1997) An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. Eur J Anaesthesiol 14: 215-219.
33. Hajsadeghi S, Jafarian Kerman SR, Pouraliakbar H, Mohammad M (2012) A huge coronary artery aneurysm in osteogenesis imperfecta: a case report. Acta Med Iran 50: 785-788.
34. Oakley I, Reece LP (2010) Anesthetic implications for the patient with osteogenesis imperfecta. AANA J 78: 47-53.
35. Forlino A, Cabral WA, Bames AM, Marini JC (2011) New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol 7: 540-557.
36. Marini JC, Letocha AD, Chemoff EJ (2005) Osteogenesis Imperfecta. In S. B. Cassidy and J. E. Allanson (Eds). Management of genetic syndromes. Hoboken NJ: Wiley.
37. Haidar R, Musallam KM, Taheer AT (2011) Bone disease and skeletal complications in patients with thalassemia major. Bone 48: 425-432.
38. Karimi M, Ghiam AF, Hashemi A, Alinejad S, Soweid M, et al. (2007) Bone mineral density in beta-thalassemia major and intermedia. Indian Pediatr 44: 29-32.
39. Graziani F, Cei S, Guerrero L, Maldague B, Nagant de Deuxchaisnes C (1987) Radiological manifestations of bisphosphonates treatment with APD in a patient with osteogenesis imperfecta. Am J Kidney Dis 25: 29-32.
40. Haynes M, Parker G, Ell J, Sillence D (1999) Basilar Impression complicating osteogenesis imperfecta type IV: Clinical and neuroradiological findings in four cases. J Neurol Neurosurg Psychiatry 66: 357—364.
41. http://www.hindawi.com/journals/gri/2011/983942/
42. Elliott D, Rezai KA, Dass AB, Lewis J (2003) Management of retinal detachment in osteogenesis imperfecta. Arch Ophthalmol 121: 1062-1064.
43. Rauch F, Travers R, Plotkin H, Glorieux FH (2002) The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. J Clin Invest 110: 1293-1299.
44. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH (2006) Vertebral morphometry in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate treatment. Bone 39: 901-906.
45. Gatti D, Rossini M, Viapiana O, Idolazzi L, Adami S (2013) Clinical development of neridronate: potential for new applications. Ther Clin Risk Manag 9: 139-147.
46. Mhaskar R, Redzepovic J, Wheatley K et al (2012) Bisphosphonates in multiple myeloma: a network meta-analysis. Cochrane Database Syst Rev 5: CD003188.
47. Mackiewicz-Wysocka M, Pankowska M, Wysocki PJ (2012) Progress in the treatment of bone metastases in cancer patients. Expert Opin Investig Drugs 21: 785-795.
48. Iwamoto S, Sato Y, Uzawa M, Matsumoto H (2013) Eleven years of experience with bisphosphonate plus alfacalcidol treatment in a man with osteogenesis imperfecta type I. Ther Clin Risk Manag 9: 1-7.
49. Chahine C, Cheung MS, Head TW et al (2008) Tooth extraction socket healing in pediatric patients treated with intravenous pamidronate. J Pediatr 153: 719-720.
50. Hennedige AA, Jayasinghe J, Khajeh J, Macfarlane TV (2014) Systematic review on the incidence of bisphosphonate related osteonecrosis of the jaw in children diagnosed with osteogenesis imperfecta. J Oral Maxillofac Res 4: e1.
51. O’Sullivan ES, van der Kamp S, Kilbane M, McKenna M (2014) Osteogenesis imperfecta in adults: phenotypic characteristics and response to treatment in an Irish cohort. Ir J Med Sci 183: 225-230.
52. Phillips CA, Remington TD, Steiner RD (2008) Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev 4: CD005988.
53. Hald JD, Evangelou E, Langdahl BL, Ralston SH (2015) Bisphosphonates for the prevention of fractures in osteogenesis imperfecta: meta-analysis of placebo-controlled trials. J Bone Miner Res 30: 929-933.
54. Devogelaer JP, Malghem J, Maldague B, Nagant de Deuxchaisnes C (1987) Radiological manifestations of bisphosphonates treatment with APD in a children suffering from osteogenesis imperfecta. Skeletal Radiol 16: 360-363.
55. Rauch F, Travers R, Glorieux FH (2006) Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. J Clin Endocrinol Metab 91: 511-516.
56. Adami S, Gatti D, Colapietro F, Fraucci E, Braga V, et al. (2003) Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res 18: 126-130.
57. Antoniazzi F, Monti E, Venturi G, Franceschi R, Doro F, et al. (2010) GH in combination with bisphosphonate treatment in osteogenesis imperfecta. Eur J Endocrinol 163: 479-487.
58. Gutta R, Louis PJ (2007) Bisphosphonates and osteonecrosis of the jaws: science and rationale. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104: 186-193.
59. Nee RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344: 1434—1441.
60. Hoyer-Kuhn H, Semler O, Stark C et al (2014) A specialization rehabilitation science and rationale. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104: 186-193.
61. Pagliaro CA, Remmington T, Steiner RD (2008) Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev 4: CD005988.
62. Hald JD, Evangelou E, Langdahl BL, Ralston SH (2015) Bisphosphonates for the prevention of fractures in osteogenesis imperfecta: meta-analysis of placebo-controlled trials. J Bone Miner Res 30: 929-933.
63. Devogelaer JP, Malghem J, Maldague B, Nagant de Deuxchaisnes C (1987) Radiological manifestations of bisphosphonates treatment with APD in a children suffering from osteogenesis imperfecta. Skeletal Radiol 16: 360-363.
64. Rauch F, Travers R, Glorieux FH (2006) Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. J Clin Endocrinol Metab 91: 511-516.
65. Adami S, Gatti D, Colapietro F, Fraucci E, Braga V, et al. (2003) Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res 18: 126-130.
66. Antoniazzi F, Monti E, Venturi G, Franceschi R, Doro F, et al. (2010) GH in combination with bisphosphonate treatment in osteogenesis imperfecta. Eur J Endocrinol 163: 479-487.
67. Gutta R, Louis PJ (2007) Bisphosphonates and osteonecrosis of the jaws: science and rationale. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104: 186-193.
68. Nee RM, Arnaud CD, Zanchetta JR et al (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344: 1434—1441.
69. Hoyer-Kuhn H, Semler O, Stark C et al (2014) A specialization rehabilitation science and rationale. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104: 186-193.
70. Pagliaro CA, Remmington T, Steiner RD (2008) Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev 4: CD005988.
74. Hoyer-Kuhn H, Semler O, Schoenau E (2014) Effect of denosumab on the growing skeleton in osteogenesis imperfecta. J Clin Endocrinol Metab 99: 3954-3965.

75. Le Blanc K, Gotherstrom C, Rindgen O, Hassan M, McMahon R et al (2005) Fetal mesenchymal stem cells engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation 79: 1607—1614.

76. Deyle DR, Khan IF, Ren G, Wang PR, Kho J, et al. (2012) Normal collagen and bone production by gene-targeted human osteogenesis imperfecta iPSCs. Mol Ther 20: 204-213.

77. Atkinson SD, McGilligan VE, Liao H, Szeverenyi I, Smith EJ et al (2011) Development of allele- specific therapeutic siRNA for keratin 5 mutations in epidermolysis bullosa simplex. Journal of Investigative Dermatology 131: 2079—2085.

78. Carroll JB, Warby SC, Southwell AL, Doty CN, Greenlee S et al (2011) Potent and selective antisense oligonucleotides targeting single- nucleotide polymorphisms in the Huntington disease gene/ allele- specific silencing of mutant huntingtin. Molecular Therapy 19: 2178—2185.

79. Lindahl K, Langdahl B, Ljunggren Ö, Kindmark A (2014) Treatment of osteogenesis imperfecta in adults. Eur J Endocrinol 171: R79-90.

80. Chan JK, Gótherström C (2014) Prenatal transplantation of mesenchymal stem cells to treat osteogenesis imperfecta. Front Pharmacol 5: 223.

81. Horwitz EM, Gordon PL, Koo WK et al (2002) Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: implications for cell therapy of bone. Proc Natl Acad Sci USA 99: 8932—8937.

82. Li F, Wang X, Niyibizi C (2010) Bone marrow stromal cells contribute to bone formation following infusion into femoral cavities of a mouse model of osteogenesis imperfecta. Bone 47: 546-555.

83. Vanleeene M, Saldaña Z, Cloyd KL et al (2011) Transplantation of human fetal blood stem cells in the osteogenesis imperfecta mouse leads to improvement in multiscale tissue properties. Blood 117: 1053—1060.

84. Bargman R, Posham R, Boskey AL, DiCarlo E, Raggio C et al (2012) Comparable outcomes in fracture reduction and bone properties with RANKL inhibition and alendronate treatment in a mouse model of osteogenesis imperfecta. Osteoporos Int 23: 1141—1150.

85. Sinder BP, Eddy MM, Ominsky MS, Caird MS, Marini JC, et al. (2013) Sclerostin antibody improves skeletal parameters in a Brtl/+ mouse model of osteogenesis imperfecta. J Bone Miner Res 28: 73-80.

86. Sinder BP, White LE, Salemi JD et al (2014) Adult Brtl/+ mouse model of osteogenesis imperfecta demonstrate anabolic response to sclerostin antibody treatment with increased bone mass and strength. Osteoporos Int. 25: 2097—2107.

87. Grafte I, Yang T, Alexander S et al (2014) Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta. Nat Med 20: 670—675.