Osteogenesis imperfecta: clinical assessment and medical treatment

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Osteogenesis imperfecta (OI) is a phenotypically and molecularly heterogeneous group of heritable connective tissue disorders characterized by low bone mineral density, recurrent fractures, and bone deformities. Most cases of OI are inherited in an autosomal dominant manner and are caused by mutations in the COL1A1 and COL1A2 genes, leading to quantitative or qualitative defects in type I collagen. More recently, a number of other genes responsible for both recessive and dominant forms of this condition have been identified. In this brief review, we discuss current understanding of clinical assessment, follow-up and pharmacological therapies for the treatment of OI. The multidisciplinary surveillance in patients with OI includes periodical hearing and vision testing, dental examination, spirometry or body plethysmography, evaluation of heart/valvular function, and neurological and psychological assessment. There is a need for regular assessment of bone mineral density (BMD) to evaluate treatment success and disease progression, and skeletal radiographs at the time of diagnosis and later as indicated by orthopaedists. Treatment of OI is aimed at preventing or controlling the symptoms present in individual patient with the main goals to decrease fracture rate, relieve bone pain, and provide sufficient bone mass and good muscle strength promoting self-mobility and growth. This requires a multi-disciplinary approach, utilizing medical treatment, physical therapy, orthopedic surgery, and nutrition monitoring. Intravenous bisphosphonate therapy is the most widely used medical treatment. It has an evident effect on BMD of lumbar spine, femoral neck and total hip in growing children and can lead to vertebral reshaping after compression fractures, but no significant effect on the risk of fractures has been observed in adults. Other novel promising therapies include teriparatide, combination therapy with antiresorptive and anabolic drugs, denosumab, transforming growth factor beta, sclerostin and cathepsin K inhibitors, and cell-based therapy, such as bone marrow or mesenchymal stem cell transplantation. Gene targeting approaches are still at early stages of investigation.

**Key words:** children, fractures, osteogenesis imperfecta, bone mineral density, bisphosphonates, denosumab, teriparatide, mesenchymal stem cell, transforming growth factor beta, sclerostin antibody, growth hormone

**INTRODUCTION**

Osteogenesis imperfecta (OI), often called „brittle bone disease”, is an inherited heterogeneous group of connective tissue disorders most frequently affecting type I collagen, which results in increased bone fragility and recurrent fractures (1-3). The majority of OI patients have an autosomal dominant heterozygous mutation in the COL1A1 (17q21.31-q22) or COL1A2 (7q22.1) gene that affects one of the two α-chains of type I collagen (6-8). Phenotype presentations, as well as severity of the disorder in affected patients depend on the type of mutation, e.g., mutations in COL1A1/2 may lead to a decreased amount of normal collagen presenting with mild phenotype (OI type I) or may disrupt the
Clinical manifestations vary greatly from patient to patient, even among the same type or subtype of OI and even within members of the same family. The majority of OI cases (possibly 85%-90%) are caused by an autosomal dominant mutation in a gene coding for type 1 collagen (types I, II, III and IV; see in Table 1). Types V and IX are caused by the genes that interfere with collagen production and are inherited in a recessive manner (14). These new forms of OI are presented with moderate to severe clinical features (patients have an increased number and frequency of fractures, mild to moderate bone deformities, kyphoscoliosis, and variable short stature, some are immobile and require wheelchair) (9). Generally, severely affected patients suffer multiple fractures with minimal or no trauma, and infants with the worst form of OI die at birth or shortly after because of respiratory complications (15). Mild forms of OI may be manifested only by premature osteoporosis or severe postmenopausal bone mineral loss (16). Clinical assessment of patients with OI is complex and challenging due to the heterogeneity both across and within different types. There is no single biomarker or clinical characteristic that can recognize, evaluate or monitor patients with OI. In clinical assessment, it is important to establish timely diagnosis to initiate treatment as early as possible to prevent progression and complications of the disease (17, 18). The diagnosis is usually easy to establish in patients with positive family history, bone fragility, and expressed extra-skeletal manifestations (7, 15). However, in the absence of these manifestations, making diagnosis may be difficult.

### Table 1. Clinical features in osteogenesis imperfect (OI) types, adapted and extended classification of OI by Sillence et al. (12)

<table>
<thead>
<tr>
<th>Type</th>
<th>Genetic</th>
<th>Bone fragility / deformity</th>
<th>Teeth</th>
<th>Sclera</th>
<th>Spine</th>
<th>Hearing</th>
<th>Cardio-respiratory complications</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>AD</td>
<td>Variable, less severe than other types, deformity moderate</td>
<td>Normal</td>
<td>Blue</td>
<td>Scoliosis and kyphosis in 20%</td>
<td>Possible hearing loss (early twenties or thirties)</td>
<td>Usually absent Possible in patients with kyphoscoliosis</td>
<td>Fair</td>
</tr>
<tr>
<td>IB</td>
<td>AD</td>
<td>Normal/na?</td>
<td>Dentinogenesis imperfecta</td>
<td>NA</td>
<td>NA</td>
<td>Possible</td>
<td>Sbsent</td>
<td>NA</td>
</tr>
<tr>
<td>II</td>
<td>AD</td>
<td>Very severe/multiple fractures</td>
<td>Unknown</td>
<td>Blue</td>
<td>NA</td>
<td>NA</td>
<td>Frequently causing death at birth</td>
<td>Perinatal death</td>
</tr>
<tr>
<td>III</td>
<td>AD</td>
<td>Severe/progressive bowing of long bones and spine</td>
<td>Dentinogenesis imperfecta</td>
<td>Bluish at birth, white in adults</td>
<td>Kyphoscoliosis</td>
<td>Possible</td>
<td>Possible</td>
<td>Wheelchair bound, not ambulatory</td>
</tr>
<tr>
<td>IVA</td>
<td>AD</td>
<td>Moderate</td>
<td>Normal</td>
<td>White or near-white</td>
<td>Kyphoscoliosis</td>
<td>Possible</td>
<td>Possible</td>
<td>Fair</td>
</tr>
<tr>
<td>IVB</td>
<td>AD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>V-IX</td>
<td>AD or AR (VII-IX)</td>
<td>Similar to type IV or type II, moderate to severe, distinctive histology</td>
<td>Dentinogenesis imperfecta</td>
<td>White</td>
<td>Kyphoscoliosis in some to NA</td>
<td>Hearing loss in some</td>
<td>Possible to severe</td>
<td>Wheelchair bound to death (VII and VIII)</td>
</tr>
</tbody>
</table>

NA = not applicable; AD = autosomal dominant; AR = autosomal recessive
Extra-skeletal features can be subclinical (e.g., hearing loss) (11, 14, 16), nonspecific (e.g., dark or bluish sclera in infants), or more clearly expressed at certain ages (e.g., dentinogenesis imperfecta more pronounced in primary than in permanent dentition) (16).

Patients with OI should undergo regular multidisciplinary surveillance for potential intervention, so that appropriate intervention is initiated as soon as possible (18). Optimal management of OI in children and later in adults requires a multidisciplinary approach involving different paediatric subspecialists (e.g., pulmonologist, cardiologist, endocrinologist, geneticist), orthopaedic surgeon, endocrinologist, rehabilitation specialist, dentist, psychologist, physiotherapist, and occupational therapist (19). In the clinical assessment and monitoring of patients with OI, the following is recommended:

- **Assessment of bone mineral density (BMD) by dual-energy absorptiometry (DXA)** is the standard and most widely used method to measure bone density (usually lower spine, hips, and wrist). If possible, DXA scans should be done using the same machine each year to avoid variations in test results caused by different equipment. BMD is related to disease severity (functional outcome, rate of fractures, and rate of surgery) and/or initiated pharmacological therapies (20). Children receiving bisphosphonate (BP) treatment should have yearly (or more frequently as clinically indicated) assessment of BMD and radiologic assessment of long bones and spine to determine the effect of treatment on vertebral geometry, long-bone fractures, and changes in bone mass (21).

- **Bone biopsy** has been used as an invasive diagnostic procedure and is an important method in the research of OI and other metabolic bone diseases. Bone biopsy is not a regular diagnostic method or procedure performed in regular monitoring of patients with OI. When feasible, a biopsy of the iliac bone can identify all types of OI. Bone biopsy is invasive, requiring specially trained personnel, general anaesthesia, and the child must weigh at least 10 kg. A bone biopsy may be obtained during orthopaedic surgery.

- **Skeletal radiographs** should be performed at the time of diagnosis and then every 1-2 years (or sooner if clinically indicated) in cooperation with orthopaedists (20). Discrepancies in leg length can be caused by fractures or problems with growth plates. These discrepancies need to be evaluated by a gait specialist, most commonly orthopaedist, to prevent the child from losing the ability to walk. The goals of orthopaedic assessment include fracture care and prevention or correction of bone deformities.

- **Hearing test** to evaluate conductive and sensorineural hearing loss in cooperation with the ENT specialist. Hearing test (formal audiology) is recommended initially at nine months of age and then at regular intervals (22, 23).

- **Vision screening every 2-3 years**, with referral to an ophthalmologist as indicated by clinical findings (24).

- **Spirometry or body plethysmography** to monitor for restrictive disturbances of ventilation secondary to rib and vertebral fractures or spine/rib deformities, every 1-2 years if clinically indicated, particularly in patients with moderate to severe OI. Patients with OI type III or other moderate to severe types of OI should have yearly pulmonary ventilation tests (25).

- **Cardiovascular system involvement** in patients with OI can occur even without the presence of clinical manifestations. In the assessment of cardiovascular complications, electrocardiogram and echocardiogram should be performed every two years to detect aortic root dilatation and valvular dysfunction (26). A small number of adults with OI have heart valve problems, the most common being mitral valve prolapse. Dilation of the aorta may also occur but is not common. If the OI patient is suspected to have developed cardiovascular complications such as aortic dilatation, it is recommended to perform additional diagnostics such as magnetic resonance imaging (MRI) of the heart and large blood vessels, and to order more frequent follow-up visits (27).

- **Neurologic examination** should be part of regular management of OI patients. Basilar skull deformity could lead to basilar invagination, as indicated by symptoms or behavioural changes, particularly in patients with type III OI or similar phenotype (types VII to IX) (28).

- **Developmental assessment** (primary care paediatrician) with referral to early intervention specialists for those younger than three years and referral to physical and occupational therapy for those older than three years of age (29). A child's large muscle development in patients with OI may be affected by fractures, muscle weakness, abnormal body size, shape and proportion, misalignment of long bones and joints. Some types of OI are characterized by significantly short stature (2, 7). Since OI has a significant effect on growth (and development), especially during puberty, it is important to include endocrinologist in the multidisciplinary team for clinical assessment of OI patients.

- **Psychological assessment** should be performed routinely in all infants with OI and their families within the first few months of life, and later on regular basis. The psychologist can identify patients and families likely to be at an increased risk of developing psychological difficulties in order to offer preventive intervention (17, 30, 31).

- **Dietetic assessment** is particularly recommended to more severely affected infants with feeding problems.
(e.g., weak sucking reflex, gastroesophageal reflux, or lung aspiration problems) and older children with limited mobility and poor or unhealthy diet. Dietitian can suggest dietary modifications and develop nutritional care plans to help infants and children develop a healthy lifestyle diet that supports optimal bone mass, muscle strength, and aiming at avoiding obesity (17, 29).

- **Dental assessment as indicated for dentinogenesis imperfecta.** Dentinogenesis imperfecta is evident in approximately 50% of patients with OI and is characterized by transparent, discoloured and fragile teeth that fracture easily. Dental abnormalities are usually apparent when the first tooth erupts (31). Patients with OI require dutiful oral hygiene and frequent follow-up by a paediatric dentist who is familiar with the disorder.

- **Assessment of coagulopathy (bleeding time and coagulation tests) before any surgical procedure should be performed in all patients with OI.** The bleeding diathesis associated with OI related to capillary fragility and abnormalities of platelet function results in a significant risk of haemorrhage during or after surgery. Large-bone intravenous access should be obtained before major surgical procedures to allow for rapid administration of fluid and blood products. In addition, nonsteroid anti-inflammatory drugs should probably be avoided because of their antiplatelet effects (32).

- **Hyperthermia may occur in patients with OI for unclear reasons, but these patients are not at an increased risk of malignant hyperthermia (21).**

- **Biochemical and hormonal laboratory parameters of bone and mineral metabolism such as serum and urine calcium, serum phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) are usually normal in patients with mild type of OI (2,7,16).** Some abnormalities have been reported, e.g., elevated levels of serum ALP (OI type VI) (34), or hypercalciuria, which reflects the severity of bone disease. The children with hypercalciuria were of shorter stature and had a greater lifelong fracture rate compared with OI children with normal urinary calcium excretion (35). Monitoring the levels of vitamin D (measured as 25-hydroxyvitamin D, 25(OH)D) is also important in the management of OI patients. Over the last decade, there has been increasing awareness of the role of vitamin D in bone health. Specific data suggest that vitamin D insufficiency was observed in 80% of children with osteopenia or osteoporosis (36). Several of published data assessing vitamin D status in paediatric OI patients demonstrated a positive association between 25(OH) D levels and lumbar spine areal bone mineral but no clear evidence for association between other markers of bone mineralization, bone metabolism or bone mass in children with OI (37). OI adults with short stature may require less calcium and vitamin D supplements than usually prescribed. Supplemental vitamin D intake should not exceed 800 IU/day (38).

**TREATMENT**

Treatment of OI is aimed at preventing or controlling the symptoms present in individual patient. The main goals of treatment are to decrease fracture rate, relieve bone pain, and provide bone mineral mass and muscle strength in order to achieve as long as possible normal self-mobility and linear growth. This requires a multidisciplinary approach, utilizing pharmacological treatment, physical therapy, orthopaedic surgery, and nutrition monitoring.

**Pharmacological treatment**

Pharmacological treatment includes primarily analgesics and bone-strengthening drugs, such as BPs. Intravenous BPs are currently the principal medical treatment of children with moderate to severe OI. The mechanism of BP activity is based on adhesion to mineralized surfaces and inactivation of osteoclasts, leading to the inhibition of bone resorption and increase of BMD. Although often used, BPs only slow the progression of the symptoms and have no effect on OI pathogenesis.

It is known that BPs increase BMD, height and shape of the vertebral column. In addition, some studies have shown that the frequency of fractures, and possibly pain, is reduced, while muscle strength and mobility are improved (13, 39, 40). However, it has been difficult to confirm all of these findings in randomized trials. A systematic study on the efficacy of treatment with BPs has confirmed that oral and intravenous administration equally increases BMD, but it has not been conclusively confirmed that the number of fractures is reduced or that treatment improves clinical status, i.e. reduces pain, increases linear growth, or improves mobility (21). Additionally, a recent meta-analysis of placebo-controlled trials suggests that the effects of BPs on fracture prevention are inconclusive (41). These studies point to the fact that BMD reduction does not imply per se a reduction in the number of fractures or improvement in other clinical outcomes.

In contrast, some recent studies still confirm clinical efficacy of BP administration but only in children. A Swedish study showed that pamidronate treatment in children with all types of OI increased lumbosacral BMD, decreased fracture rate, and improved healing of vertebral compression fractures. Fracture reduction was prompt and maintained during treatment, irrespective of age at treatment initiation and
cal bone samples from children with OI treated with BPs investigating structural and mechanical properties of cortical bone. The parathyroid hormone is effectively applied in post-menopausal osteoporosis because it has anabolic effect on collagen I mutation type (42). Long-term intravenous or oral BP treatment has positive effects on lumbar spine, femoral neck and total hip BMD, bone turnover markers and fracture risk, with a good safety profile in children (43, 44), but no significant effect on the risk of fractures was observed in adults (45, 46). These findings are supported by a meta-analysis of nine randomized controlled trials including 557 patients, demonstrating that BPs were efficacious in reducing fractures in children, whereas in adults the effect of administering BPs was equivalent to placebo (47).

While the efficacy of BP treatment does not seem to be related to the genotype of type I collagen in patients with OI (48), therapeutic success might also depend on the type of OI. Patients with OI type VI who received intravenous BP treatment during linear growth (total duration of BP treatment between 1.6 and 13.8 years, median 8.3 years) had an increase in lumbar spine areal BMD, a higher final height z-score, and showed reshaping of vertebral bodies, but major problems such as high fracture rates of lower extremities, scoliosis, and restricted mobility function persisted in most patients (49).

The decision to initiate BP administration is based on the severity of clinical manifestations, patient age, and ability to manage oral or intravenous administration (50). Different treatment protocols are in use. Decision on the type and mode of BP administration is made in agreement with the parents. Because of the long half-life of BPs and the risk of adynamic bone, it is important to use the lowest effective cumulative dose to improve bone density and vertebral geometry (51). It is possible to adjust the dose individually, depending on the response to treatment. Duration of treatment, interval between cycles, and dose titration are still topics of studies. The maximum benefit of BPs is seen in the first two to four years of treatment, after which it seems that there is little further improvement (52). Therefore, a regimen in which children are treated with pamidronate for 3 years, then followed carefully for fractures, bone density and vertebral geometry over subsequent years is favoured by some experts (51). Bone metabolism is suppressed for 2 years after BP discontinuation. Although bone mass gain continues after cessation of treatment, BMD in lumbar spine increases less than in healthy individuals (53).

Treatment with BPs still raises concerns. BP anti-absorption activity prevents normal remodelling necessary for bone restoration. It is unknown whether these changes in bone formation can have significant adverse effects. There is a concern related to the danger of micro-fractures and calcification of cartilage, which can contribute to slower healing of the fractures and to increased bone brittleness. A study investigating structural and mechanical properties of cortical bone samples from children with OI treated with BPs showed that the microstructure was impaired. The higher porosity and osteocyte lacunar density negatively impacted the mechanical properties and made the bone more prone to fractures (54). Additionally, atypical fractures have been reported in children with OI treated with BPs (55). Although there is no clear evidence for slower bone healing after a fracture, there is evidence for a significant delay in osteomy recovery after surgical procedures. Treatment is not recommended for 4-6 months after osteotomy, when x-rays show a satisfactory healing process. Delayed osteotomy healing occurs less frequently in the past 10 years than in the decade before that. It is likely that this is attributable to the improvement in both medical and surgical management (56).

After discontinuation of BP treatment in children, the new bone forming at the bone growth plate is less dense. It is believed that the junction between treated bone and new bone is prone to stress leading to new fractures. For this reason, some experts recommend maintenance therapy until the end of linear growth (57).

Osteonecrosis is often referred to as a complication associated with BP treatment. This phenomenon was largely observed in elderly patients with cancer who were on BP therapy. To date, however, there have been no cases of osteonecrosis of the jaw in patients with OI (58).

In a recent systematic review that included randomized controlled trials assessing the effects of BPs in children with OI, the most frequently reported adverse events were gastrointestinal complaints, fever, and muscle soreness (59). Muscle and bone pain reported by some patients with OI are considered important side effects that may limit BP use in a subset of patients (60). On the other hand, many studies report on a significant decrease in bone pain during BP treatment (59).

It should be kept in mind that the half-life of BP breakdown in bones is at least ten years and that their long-term effect is unknown, which is especially important in children and women of reproductive age (60).

In conclusion, although BPs are effective in treating osteoporosis, the benefit of their use in OI in relation to undesirable side effects is still questionable. As BPs are currently extensively used for long-term treatment of OI, additional research is needed to determine the best and safest way of their use and to evaluate long-term efficacy in reducing fractures and improving the patient quality of life.

Teriparatide

The parathyroid hormone is effectively applied in postmenopausal osteoporosis because it has anabolic effect on...
the bone. Clinical trials with teriparatide (PTH 1-34), an active part of the endogenous human parathyroid hormone (PTH), in adults with OI have shown that teriparatide has anabolic effect in the mild form of OI. It increases BMD in the hip, spine and vertebra, and improves estimated vertebral strength (61). However, teriparatide did not lead to a significant reduction in the number of fractures, or other clinical effects. Its use in children is still not recommended because there is evidence from experiments that it causes osteosarcoma in young rats (57).

**Growth hormone**

Growth hormone (GH) has anabolic effects on bone. It has long been considered that GH administration could be of benefit for patients with OI, but it has been shown that GH increases bone turnover, which is harmful for OI patients. In addition, children with OI present on average with normal insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3) levels (62). Still, there is evidence for the positive effect of GH on BMD and on growth rate in about half of the treated patients (63). A 1-year randomized controlled study showed that GH would increase the rate of linear growth in a subgroup of patients and that it might be effective in combination with BP therapy, but there was no improvement in fracture rate (64).

**Denosumab**

Denosumab, a monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), has emerged as an important novel therapy for OI. A 48-week, open-label, pilot study of the safety and efficacy of denosumab administered subcutaneously every 12 weeks in a dose of 1 mg/kg body weight in 10 children with OI suggests that denosumab may be beneficial in decreasing bone turnover and increasing BMD. No severe side effects were noted (65). However, data in paediatric patients are limited. At present, there are safety concerns related to rebound increase of bone turnover and impaired mineral homeostasis that limit the use of denosumab in children (66). Additional studies are needed to determine if and how these effects can be mitigated (67).

**Recent medical treatment options**

New pharmacological treatments showing promising results are currently being under investigation. An excellent review summarizes different therapeutic options including antiresorptive agents, anabolic treatment, and gene- and cell-therapy approaches (68).

Transforming growth factor beta (TGF-β) is a protein important in bone formation. It is well-known that TGF-β, which is produced by osteoblasts, has a capacity to modify bone remodelling by coupling the activity of bone resorbing osteoclasts with bone forming osteoblasts (69). In studies on mice with OI, it has been shown that silencing TGF-β can lead to higher bone mass, quality and strength (70). Fresolimumab is an antibody that can silence TGF-β. A study designed to determine if fresolimumab is safe in the treatment of OI is currently under way (ClinicalTrials.gov Identifier: NCT03064074).

Sclerostin is a naturally occurring protein encoded by the SOST gene and produced almost exclusively by osteocytes. It inhibits bone formation by binding to the low-density lipoprotein receptor related protein 5 and 6 on osteoblasts. Sclerostin also leads to down-regulation of phosphate regulating endopeptidase homologue X-linked (PHEX). PHEX degrades peptides that bind to nascent bone mineral and inhibit mineral deposition. Therefore, down-regulation of PHEX results in decreased bone mineralization (71). Additionally, sclerostin inhibits canonical Wnt signalling pathway, an important regulator of bone mass that induces osteoblastogenesis and bone formation, and suppresses osteoclastogenesis and bone resorption (72). Experiments with a variety of animal models have shown that inhibition of sclerostin results in increased bone formation and reduced bone resorption (73). A recent study has shown that a combination of sclerostin antibody and zoledronic acid treatment outperforms either treatment alone in a mouse model of OI (74). The short-term, open-label, phase 2a trial aimed to evaluate the pharmacodynamics and safety of multiple, escalating infusions of BPS804, a neutralizing, anti-sclerostin antibody, indicates that BPS804 stimulates bone formation, reduces bone resorption, and increases lumbar spine BMD in adults with moderate OI (75).

Cathepsin K inhibition results in reduction of the enzymatic resorption process of the extracellular matrix by mature osteoclasts (76). In comparison with BPs, the effect of cathepsin inhibitors is transient and reversible (77). However, cathepsin inhibitors have not yet been studied in patients with OI. Additional concerns are raised because it was found that treatment might be associated with an increased risk of cerebrovascular accidents (78).

Cell-based therapy, such as bone marrow or mesenchymal stem cell transplantation, has also been investigated. Transplantation of human foetal mesenchymal stem cells has been proposed as skeletal anabolic therapy to enhance bone formation. Intraperitoneal injection of human amniotic mesenchymal stem cells into a mouse model of OI reduced fracture susceptibility, increased bone strength, improved bone quality and micro-architecture, normalized bone remodelling, and reduced TNFα and TGFβ signalling. Donor cells engrafted into bones, differentiated into osteo-
blasts and promoted endogenous osteogenesis and maturation of resident osteoblasts (79).

Other therapies including gene targeting approaches are under evaluation. A promising option could be gene silencing through RNA interference (80).

Abbreviations

ALP - alkaline phosphatase
BMD - bone mineral density
BPs - bisphosphonates
DXA - dual-energy absorptiometry
ENT - ear, nose and throat
GH - growth hormone
IGF-I - insulin-like growth factor-1
IGFBP-3 - insulin-like growth factor binding protein-3
MRI - magnetic resonance imaging
OI - osteogenesis imperfecta
PTH - parathyroid hormone

REFERENCES


Osteogenesis imperfecta (OI) je fenotipski i molekularno heterogena skupina nasljednih bolesti veziva obilježena smanjenom gustoćom kostiju, čestim lomovima i deformacijama. Većina OI-a nasljeđuje se autosomno dominantno i uzrokovana je mutacijama u genima COL1A1 i COL1A2, što dovodi do kvantitativnog ili kvalitativnog defekta kolagena tip 1. U posljednje vrijeme otkriven je veći broj gena koji su odgovorni za recesivne i dominantne oblike ove bolesti. U ovom kratkom pregledu razmatramo suvremeni pristup kliničkoj dijagnostici i praćenju te farmakološkom liječenju OI-a. Multidisciplinsko praćenje bolesnika uključuje povremeno testiranje sluha i vida, stomatološke preglede, spirometriju ili pletizmografiju, evaluaciju funkcije srca/valvula, neurološke i psihološke kontrole. Potrebno je redovito pratiti vrijednosti gustoće kostiju (BMD) kako bi se utvrdio uspjeh liječenja i progresija bolesti, a nužne su i rengenske slike kostiju kod postavljanja dijagnoze i kasnije prema indikaciji ortopeda.

Svrha liječenja je i da spriječi ili suzbije simptome prisutne kod pojedinog bolesnika, a glavni ciljevi su smanjiti broj lomova, suzbiti bol, poboljšati koštanu masu i mišićnu snagu te osigurati samostalnu pokretnost i rast. To zahtijeva multidisciplinski pristup u liječenju lijekovima, fizičkom terapijom, kirurškim ortopedskim zahватima i odgovarajućom prehranom. Intravenska primjena bisfosfonata je najšire primjenjiv oblik medicamentoznog liječenja. Ona ima očit učinak na BMD slabinske kralježnice, vrata bedrene kosti i kukova djece u rastu, te može dovesti do preoblikovanja kralježaka nakon kompresijskih fraktura, ali nema značajnijeg učinka na rizik pojave lomova kod odraslih osoba. Druge nove obećavajuće terapije uključuju teriparatid, liječenje kombinacijom antiresorptivnih i anaboličnih lijekova, denosumab, inhibiciju TGF-β (eng. transforming growth factor beta), sklerostina i kathepsina K te staničnu terapiju, poput transplantacije koštane srži ili mezenimalnih stanica. Genska terapija je još u ranim stadijima ispitivanja.

**Ključne riječi:** djeca, frakture, osteogenesis imperfecta, mineralna gustoća kostiju, bisfosfonatei, denosumab, teriparatid, mezenimalne matične stanice, transformirajući čimbenik rasta beta, protutijelo na sklerostin, hormon rasta