

Osteogenesis imperfecta - multi-systemic and life-long disease that affects whole family

Primorac, Dragan; Antičević, Darko; Barišić, Ingeborg; Hudetz, Damir; Ivković, Alan

Source / Izvornik: **Collegium Antropologicum, 2014, 38, 767 - 772**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:744854>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2024-07-12**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



Osteogenesis Imperfecta – Multi-Systemic and Life-Long Disease that Affects Whole Family

Dragan Primorac¹⁻⁴, Darko Antičević^{5,6}, Ingeborg Barišić⁷, Damir Hudetz^{3,8} and Alan Ivković^{3,8,9}

¹ University of Split, School of Medicine, Split, Croatia

² »J. J. Strossmayer« University, School of Medicine, Osijek, Croatia

³ »Sv. Katarina« Hospital, Zabok, Croatia

⁴ Penn State University, Eberly College of Science, State College, PA, USA

⁵ University of Zagreb, University Hospital Center Zagreb, Department of Orthopaedic Surgery, Zagreb, Croatia

⁶ University of Zagreb, School of Medicine, Zagreb, Croatia

⁷ Children's Hospital, Department of Clinical Genetics, Zagreb, Croatia

⁸ University Hospital »Sveti Duh«, Department of Orthopaedic Surgery, Zagreb, Croatia

⁹ University of Rijeka, Department of Biotechnology, Rijeka, Croatia

ABSTRACT

Osteogenesis imperfecta or brittle bone disease, a heritable disorder of connective tissue, is the most common of the inherited disorders primarily affecting bone. There are approximately 400 individuals with OI in Croatia alone. It is estimated that twice that number is present, represented by individuals with mild OI in whom the diagnosis has not been made. Due to the relatively low number of patients in the general population, treating physicians have limited experience with this disease, either with children or adults. The basis of this disease in European populations is mostly the result of defects in the structure or processing of collagen type I, an important protein of the extracellular matrix of many tissues. Presently, molecular defects in 16 different genes have been discovered to result in at least one type of OI of which 14 are not COL1 mutation loci. Although fractures occurring with no injury or minor injury are the hallmark of OI, other non-mineralized tissues can be affected as well and the pathological changes can be present in skin, tendons, eyes, teeth and blood vessels. Clinical manifestations are very heterogeneous and numerous signs and symptoms such as blue sclera, deafness, abnormal teeth development, joint hypermobility, increased risk of hernias, capillary fragility, aneurysms etc. Although there is no cure for this disease, there are specific therapies that can reduce the pain and complications associated with OI. The purpose of this review is to provide a brief overview of the molecular basis of this disease, describe clinical presentations, as well as to present orthopaedic therapeutic modalities for the patients with OI.

Key words: *osteogenesis imperfecta*, fractures, collagen type I

Classification and Clinical Picture

Osteogenesis imperfecta (OI) or brittle bone disease is the name for a group of heritable disorders of connective tissue which are associated with osteoporosis and variable amount of skeletal deformities^{1,2}. It is estimated that the prevalence of OI is 1 in 15,000–20,000 infants. *Osteogenesis imperfecta* is a very complex life-long disease for which pediatrician and orthopedic surgeon will play an essential role in developing a plan that optimizes the quality of life for patients. An extensive literature has grown up on this subject³⁻⁹. Clinical features of OI vary in severity, from mild to neonatal lethal forms. Bone

fragility in OI is the result of a failure of the osteoblasts to synthesize adequate amounts of normal skeletal matrix and it is important to notice that increased osteoclastic bone resorption is not responsible for the osteopenia of OI.

All forms of OI are genetic and severity depends on the specific gene defect and the quality of perinatal and postnatal care as well as the underlying genetic defect. In 1978, Sillence, classified OI into four major clinical types¹⁰. That classification was modified several times but The International Nomenclature Committee for Consti-

tutional Disorders of the Skeleton (2010) recommended that the nosology should abandon the numerical nomenclature and group OI Syndrome into 5 major clinical entities: Non-deforming OI with Blue Sclerae (OI type I), Perinatally Lethal OI (Type II), Progressively Deforming OI (Type III), Common Variable OI with Normal Sclerae (OI type IV) and OI with calcification in inter-osseous membranes (OI type V). The proposed classification is based on clinical and radiological features as well as on inheritance patterns¹¹. While genetic databases such as OMIM (On-line Mendelian Inheritance in Man) continue to give numbers as each new gene is discovered, the Nomenclature committee recommended these OMIM entities be incorporated into the clinical genetic phenotypes. The most common complications of OI related to mortality include declining pulmonary function in childhood and cor pulmonale in adulthood, both of which it is hoped are prevented by a modern approach to therapy. Basilar invagination is an uncommon but potentially fatal complication of *Osteogenesis imperfecta*.

Molecular Basis of *Osteogenesis imperfecta*

During the last years the molecular concept of OI changed from the hypothesis of a single gene disorder to that of a disorder with multiple genetic cause disorder. For decades researchers were convinced that type I collagen was exclusively responsible for this disease. Propelled by advancement in molecular genetics it has been possible to show that OI is result of different mutations at least of 16 different gene loci. However, in European populations most of the OI phenotypes are the result of different mutations affecting the collagen genes *COL1A1* and *COL1A2* genes. Collagens belonging to a family of fibrillar proteins that support almost all tissues in the body, including bone, tendon, skin, cartilage, blood vessels, sclerae, lung, dentin, heart valves, fascia, cornea, liver, etc. Collagen type I, however, is the most abundant protein in human body and is coded by two separate genes *COL1A1* and *COL1A2* that produce the pro-alpha 1 and pro-alpha 2 chains of type I collagen. Type I collagen mainly participates in building extracellular matrix of bone, dentine and skin. It is known that mutations in *COL1A1* gene are also responsible for several different health conditions including OI, Ehlers-Danlos syndrome, dermatofibrosarcoma protuberans and infantile cortical hyperostosis (Caffey disease)¹².

Autosomal Dominant OI

Heterozygous dominant negative mutations including glycine substitution mutations (the most common defect), helical splicing mutations (mainly mutations within donor or acceptor sequences of either gene has been associated with exon skipping) produce abnormalities in the sequence of different regions of the type I collagen gene and result in expression of a mutant protein that drastically affects the normal triple-helix configuration. On the other hand, quantitative mutations represented

by null allele mutations may result in a 50% reduction of total collagen mRNA, creating a mild clinical phenotype of OI. Earlier we have described that a substitution at the +1 position of donor splice site causing intron retention eventually results in an out-of-frame mRNA containing a premature termination codon^{3,9}.

The mode of inheritance in OI is almost always dominant and there is a known incidence of new mutations. The risk of an affected individual passing the mutated gene to the child is 50% while the empirical recurrence risk that clinically healthy parents are having a second child with OI is between 5–7 %¹³ as a result of parent gonadal mosaicism or recessive inheritance. Dominant inheritance of OI usually results from mutations in *COL1A1* or *COL1A2* genes (Types I–IV OI) or with a unique defect in the gene encoding osteoblast marker-interferon-induced transmembrane protein 5 (IFITM5) otherwise termed bone-restricted ifitm-like protein (Bril) (Type V OI)¹⁴.

Autosomal Recessive OI

Recent findings showed that mutations on *CRTAP*, *LEPRE1*, *PPIB*, are responsible for recessive OMIM types VII, VIII and IX respectively. Both Progressively Deforming OI and Perinatally Lethal OI may result from mutations in these genes. On the other hand defects in genes *SERPINH1* and *FKBP10*, cause autosomal recessive OMIM types X and XI OI correspondingly^{11, 12}. Most likely, recessive OI, is caused by defects in genes whose product interacts with type I collagen for either modification or /and folding. *CRTAP*, *LEPRE1* and *PPIB* genes encode components of the prolyl-3-hydroxylase complex, which can modify Pro986 in the $\alpha 1$ chains of type I collagen while *SERPINH1* and *FKBP10* encode chaperones, which may be important for proper folding of procollagen¹⁵. Additional recessive OI (Type VI OI) is related with *SERPINF1* gene that encodes pigment epithelium-derived factor (PEDF) and apparently do not have direct link to collagen, changed standard paradigm that collagen biosynthesis is primarily responsible for OI^{16,17}. Furthermore, it is believed that PEDF plays several important roles including inhibition of angiogenesis as well as endochondral bone formation. Therefore it is possible that loss of PEDF function with inactivating mutation in *SERPINF1* may result in decreasing numbers of osteoblasts and in increasing activity of osteoclasts which can initiate a decrease bone formation or enhance bone resorption. Also, we should not exclude the possibility that the PEDF has a direct role in collagen biosynthesis¹⁵. Progressively Deforming autosomal recessive *Osteogenesis imperfecta* may also result from mutations in several other genes. It is believed that the protein products of these genes interact with collagen post-translationally for folding, modification, or crosslinking, resulting in a collagen-related paradigm for OI¹⁸. Furthermore, mutation on *BMP1* (bone morphogenetic protein 1) gene was associated with OMIM Type XII OI (18). Finally, Moderately severe OI type IV or Progressively Deforming OI

may result from mutations in *SP7* gene (Zinc-finger transcription factor defect), *TMEM38B* gene (Cation Channel defect) or *WNT1* gene (WNT signaling pathway defect)¹⁸.

One of the best resources of gene variants of *COL1A1*, *COL1A2*, *BMP1*, *CRTAP*, *FKBP10*, *LEPRE1*, *PLOD2*, *PPIB*, *SERPINF1*, *SERPINH1* and *SP7* that cause OI is available at: www.le.ac.uk/genetics/collagen

***Osteogenesis Imperfecta* – Diagnosis and testing**

Dermal biopsies were the standard for OI diagnosis for many years. A diagnosis of OI is usually confirmed by biochemical analysis of the Collagen Type I polypeptides produced by cultured skin fibroblasts from the patients with OI associated mutations in *COL1A1* and *COL1A2* genes. Basically, two findings are possible, either a reduction of the amount or polypeptide produced or changes in electrophoretic mobility of one of the chains of type I collagen. Since biochemical testing requires work with fibroblast cultures it usually takes several months to investigate. Furthermore mutations which result in only a quantitative reduction in type I collagen polypeptides are not able to be simply characterized. However, genetic testing (particularly genomic DNA sequencing) is much more efficient and requires less time. Genetic diagnostic of OI after chronic villus biopsy (between 14–20 weeks) is also possible.

General and Orthopaedic Management of Patients with *Osteogenesis Imperfecta*

The main orthopaedic feature of all types of *Osteogenesis imperfecta* is increased fragility of bones. Parents of newly born child are under additional pressure due to the fact that routine child nursing could lead to their newborn long bone fracture. Those fractures and residual deformities of lower extremities are crucial obstacles for locomotion and subsequent neuromuscular development of the growing child. A significant amount of knowledge on medical and surgical treatment of OI has accumulated in the medical literature, in recent years. It is purpose of this article to present current status of genetic background as well as advances in medical and surgical treatment of OI that is available in Croatia. It is essential for the family practitioner and general physician to have sound knowledge on paradigmatic rare diseases and OI is a perfect example.

The secondary consequences of OI are hearing impairment, dental abnormalities, symptoms and signs neurological features due to macrocephaly, hydrocephalus, syringomyelia and basilar invagination (an infolding of the skull base that leads to brainstem distortion). It is obvious that multi-systemic disease requires multi specialist management approach. A fully aware physician should pay attention that in child with OI there are many potential health issues which, on the first sight, could be hidden »under the surface«. Additionally, it is

not only the child with OI who is sick, it is whole family. OI is a kind of multi-systemic disease that affects the whole normal routine life of the family.

A Team approach is a cornerstone of good medical practice in the management of OI. Treatment should be focused to the main goal i.e. to restore function to the extremities. To obtain this goal we can use careful and individualized rehabilitation and physical therapy to promote increased strength and mobility. This should be provided in specialized clinical centres for OI. Second, we could use bisphosphonates as antiresorptive pharmacological therapy. All types of OI result in fragile bones due to low quality of bone material; bone mass is diminished because bone turnover is higher resulting in less trabecular bone formed than resorbed. In addition, there is poor cortical modeling due to insufficient osteoblast performance. Also, bone geometry is distorted. It is well documented in the medical literature that bisphosphonates are useful to improve bone strength, motor function, decrease pain and improve vertebral geometry. In the most severe cases of OI cyclic intravenous administration of bisphosphonates could be introduced even before walking age. Generally, bisphosphonate treatment is indicated when the patient has more than two fractures of long bone annually and compressive fractures of vertebral bodies. However, firstly we should assess the severity of clinical manifestations in each OI patient. In Croatia, medical management with intravenous (pamidronate) or oral (alendronate) administration is possible in most major paediatric departments throughout the country.

Orthopaedic i.e. surgical treatment of fractures and deformities of lower extremity long bones is mainstay of lifelong management. Corrective surgery is crucial for ambulation due to the fact that bowed long bone soon will be fractured on the apex of bow. In the last ten years telescoping intra-medullary rods have been subject of substantial improvement¹⁹. The first version of telescoping rod i.e. Dubow-Bailey has improved version known now as Sheffield rod. The third generation of telescoping rods is Fassier-Duval (F-D) rod which has the advantage of percutaneous insertion with minimal soft tissue trauma²⁰. Specific construction of the F-D rod enables avoiding of knee and/or ankle joint arthrotomy. Telescoping rods are intra-medullary implants which are keeping long bone straight and preventing fractures²¹. One should consider intra-medullary rods as internal splints. On negative side, those rods could migrate proximally and distally^{22,23}. Some surgeons prefer to apply interlocking of distal anchorage of F-D rod as it is shown on example of tibial rodding (Figure 1).

Occasionally, one can use non-telescoping rods e.g. Kirschner wires or flexible titanium nails (Nancy) (Figure 2). This procedure could be utilized as single or double nail technique. Any type of surgery should be followed by early rehabilitation. Application of Fassier-Duval (F-D) rod is not a routine orthopaedic procedure and it is not advisable to perform it outside of specialized centre for OI patients. Currently, in Croatia, the Orthopaedic department of University of Zagreb is an institution which has all prerequisites for routine F-D telescoping rodding surgery²⁴. Brief overview of our hospital data has shown



Fig. 1. (A) Preoperative radiograph of the patient with OI. (B) Postoperative roentgenogram of the same patient after bilateral tibial corrective osteotomies with K-wires. (C) Reappearance of angular deformation two years after the surgery. (D) AP radiograph of the second corrective osteotomy with Fassier-Duval rod. (E) LL radiograph of the second corrective osteotomy with Fassier-Duval rod.



Fig. 2. Postoperative radiographs of the patient after corrective osteotomies of ipsilateral tibia (K-wire) and femur (Fassier-Duval rod).



Fig. 3. Roentgenograms of the patient three years after the corrective procedures with Fassier-Duval's intramedullary nailing.

that, up to now, one hundred and ten surgical procedures were performed in 28 patients who suffered from *Osteogenesis imperfecta*. Eleven patients (25 long-bone segments) were treated with telescoping intramedullary nail. In seven patients (18 segments) Fassier-Duval telescoping intramedullary nail was inserted. With an aim to enable patients to walk, in two of them both femurs and both tibias were corrected and protected from further fractures with third generation I-M nails i.e. Fassier-Duval (Figure 3).

Stem Cells and Gene Therapy in *Osteogenesis Imperfecta*

Since bisphosphonates cannot correct the primary cause of OI, and their long-term use and effectiveness are still uncertain, new treatment options are being devel-

oped by scientists and clinicians. Stem cells are self-renewing, multipotential cells capable of differentiating into multiple different cell types. These properties provide many advantages for the development of novel therapeutic strategies, and stem cells continue to be of unprecedented public, scientific and clinical interest. Mesenchymal stem cells (MSCs) have been particularly interesting for application in the treatment of musculoskeletal pathology since they are able to differentiate along specific tissue lineages (osteogenic, adipogenic, chondrogenic etc.), and possess trophic and immunomodulatory capabilities²⁵. Rationale for their use in the treatment of OI lays in the assumption that allogeneic transplantation of MSCs into the OI patient provides sufficient amounts of healthy osteoblasts, capable of producing normal collagen, and therefore normal bone. After first success on murine model, first clinical trial took place in late 90s^{26,27}. Child-

ren with severe type III OI were treated with transplantation of allogeneic bone marrow, which resulted in decreased number of fractures and better bone mineralization. Approximately portion of donor osteoblasts within the whole population was 1–2%. With the hypothesis that the mesenchymal component is responsible for observed effects, another study on the same patient followed. This time the patients received isolated and expanded bone marrow-derived MSCs²⁸. Similar to the first study, donor cells were detected in various tissues, including osteoblasts and skin fibroblasts producing improvement of clinical status of the patients. Unfortunately, in both of these studies, the therapeutic effect was short-termed, and the portion of healthy donor osteoblasts was relatively minor.

Gene therapy is another feasible option, relying on the observed fact the analysis of individuals who are somatic mosaics for an OI mutation but do not have evidence of active disease²⁹. Those studies suggest that the deleterious effect of OI cells can be compensated for by

the presence of normal cells. Thus, if it were possible to introduce normal cells into an individual with OI, the severity of bone disease would be reduced. To achieve these goals different strategies were employed. This process involves two steps: the inhibition of the output from the mutant collagen allele and an insertion of replacement collagen gene for the inactivated mutant gene. Once corrected, the engineered cells should be able to engraft bone, proliferate, and participate in new bone formation. The successful gene therapy heavily relies on vectors used to deliver cDNA to target cells. Viral vectors such as adenovirus, adeno-associated virus, lentivirus or retrovirus are very efficient but carry risk of immunological response or insertional mutagenesis³⁰. On the other hand, non-viral methods rely on importing naked DNA in to the cell by changing its physical and chemical properties, such as lipids, polymers and electroporation. This approach is safe, but is substantially less effective in comparison to viral vectors.

REFERENCES

- VAN DIJK FS, BYERS PH, DALGLEISH R, MALFAIT F, MAUGERI A, ROHRBACH M, SYMOENS S, SISTERMANS EA, PALS G, Eur J Hum Genet, 20 (2012) 11. DOI: 10.1038/ejhg.2011.141. — 2. SILLENCE DO, LAMANDE R, Evolution of the present understanding of the Clinical and Genetic Heterogeneity and Molecular and Biochemical Basis of Osteogenesis imperfecta. In: SHAPIRO J, BYERS P, GLORIEUX F, SPONSELLER PD (Ed) Clinical Genetics and Genomics of Osteogenesis imperfecta. Translational Medicine of Brittle Bone Diseases (Elsevier, New York, 2013). — 3. STOVER ML, PRIMORAC D, LIU SC, McKINSTRY MB, ROWE DW, J Clin Invest 92 (1993) 1994. DOI: 10.1172/JCI116794. — 4. PRIMORAC D, ROWE WD, MOTTES M, BARISIC I, ANTICEVIC D, MIRANDOLA S, GOMEZ LM, KALAJZIC I, KUSEC V, GLORIEUX FH, Croat Med J 42 (2001) 392. — 5. LIGUTIC I, BARISIC I, ANTICEVIC D, VRDOLJAK J, PRIMORAC D, Paediatr Croat 45 (2001) 19. — 6. ANTIČEVIĆ D, ZERGOLLERN LJ, JANKOVIĆ S, POTOČKI K, BARIŠIĆ I, HUZZAK N, Acta Clin Croat 41 (2002) 101. — 7. HUZZAK N, BARIŠIĆ I, REŠIĆ A, VRDOLJAK J, KUŠEC V, ANTIČEVIĆ D, Paediatrica Croatica 2 (2002) 55. — 8. VRKIĆ N, KRPAN D, PRIMORAC D, Koštane bolesti. In: TOPIĆ E, PRIMORAC D, JANKOVIĆ S (Eds.) Medicinsko-biokemijska dijagnostika u kliničkoj praksi. (Medicinska naklada, Zagreb, 2004). — 9. JOHNSON CV, PRIMORAC D, KINSTRY M MC, ROWE DW, LAWRENCE JB, J Cell Biol 150 (2000) 417. DOI: 10.1083/jcb.150.3.417. — 10. SILLENCE DO, SENN AS, DANKS DM J Med Genet 16 (1979) 101. — 11. MUNNS C, SILLENCE DO, Osteogenesis imperfecta (and Other Disorders of Bone Matrix) In: RIMOIN DL, PYERIZ RE, KORF BR (eds) Rimoin's Principles and Practices of Medical Genetics (6th Edition) (Elsevier, E-book, 2013). — 12. MARINI JC. OSTEOGENESIS IMPERFECTA. In: KLIEGMAN RM, BEHRMAN RE, JENSON HB, STANTON BS (Eds.) Nelson Textbook of Pediatrics. 19th ed. (Saunders Elsevier, Philadelphia, 2011). — 13. DE PAEPE A, SYMOENS S, MALFAIT F. Clinico-molecular findings in a cohort of 34 COL1A1/COL1A2 mutation –negative OI patients: the Ghent experience. Proceedings of 11th International Conference on Osteogenesis imperfecta, Dubrovnik, Croatia, October 2–5, 2011. — 14. MARINI JC, BLISSETT R, Clin Endocrinol Metab, 98 (2013) 3095. DOI: 10.1210/jc.2013-1505. — 15. GERMAIN-LEE LE, J Bone Miner Res, 26 (2011) 2795. DOI: 10.1002/jbmr.540. — 16. BECKER J, SEMLER O, GILSSEN C, LI Y, BOLZ HJ, GIUNTA C, BERGMANN C, ROHRBACH M, KOERBER F, ZIMMERMANN K, DE VRIES P, WIRTH B, SCHOENAU E, WOLLNIK B, VELTMAN JA, HOISCHEN A, NETZER C, Am J Hum Genet 88 (2011) 362. DOI: 10.1016/j.ajhg.2011.01.015. — 17. HOMAN EP, RAUCH F, GRAFE I, LIETMAN C, DOLL JA, DAWSON B, BERTIN T, NAPIERALA D, MORELLO R, GIBBS R, WHITE L, MIKI R, COHN DH, CRAWFORD S, TRAVERS R, GLORIEUX FH, LEE B, J Bone Miner Res 26 (2011) 2798. DOI: 10.1002/jbmr.487. — 18. MARTINEZ-GLEZ V, VALENCIA M, CAPARRÓS-MARTÍN AJ, AGLAN M, TEMTAMY S, TENORIO J, PULIDO V, LINDERT U, ROHRBACH M, EYRE D, GIUNTA C, LAPUNZINA P, RUIZ-PEREZ VL, Human mutation 33 (2012) 343. DOI: 10.1002/humu.21647. — 19. CHO TJ, CHOI IH, CHUNG CY, J Bone Joint Surg (Am) 89 (2007) 1028. DOI: 10.2106/JBJS.F00814. — 20. BIRKE O, DAVIES N, LATIMER M, LITTLE DG, BELLEMORE M, J Pediatr Orthop 31 (2011) 458. DOI: 10.1097/BPO.0b013e31821bf50. — 21. FASSIER F, SARDAR Z, AARABI M, ODENT T, HAGUE T, HAMDY R, J Pediatr Orthop 28 (2008) 799. DOI: 10.1097/BPO.0b013e31818e19b7. — 22. FORLINO A, CABRAL WA, BARNES AM, MARINI JC, Nat Rec Endocrinol 7 (2011) 540. DOI: 10.1038/nrendo.2011.81. — 23. VAN DIJK FS, PALS G, VAN RIJN RR, NIKKELS PGJ, COBBEN JM, Eu J Med Genet 53 (2010) 1. DOI: 10.1016/j.ejmg.2009.10.007. — 24. ANTIČEVIĆ D, BERGOVEC M, ĐAPIĆ T, Pediatr Croat 49 (2005) 157. — 25. IVKOVIĆ A, MARIJANOVIĆ I, HUDETZ D, PORTER RM, PEČINA M, EVANS CH Front Biosci (Elite Ed), 3 (2011) 923. — 26. PEREIRA RF, O'HARA MD, LAPTEV AV, HALFORD KW, POLLARD MD, CLASS R, SIMON D, LIVEZEY K, PROCKOP DJ, Proc Natl Acad Sci USA 95 (1998) 1142. — 27. HORWITZ EM, PROCKOP DJ, FITZPATRICK LA, KOO WW, GORDON PL, NEEL M, SUSSMAN M, ORCHARD P, MARX JC, PYERITZ RE, BRENNER MK, Nat Med 5 (1999) 309. DOI: 10.1038/6529. — 28. HORWITZ EM, PROCKOP DJ, GORDON PL, KOO WW, FITZPATRICK LA, NEEL MD, MCCARVILLE ME, ORCHARD PJ, PYERITZ RE, BRENNER MK, Blood 97 (2001) 1227. DOI: 10.1182/blood.V97.5.1227. — 29. CHAMBERLAIN JR, DEYLE DR, SCHWARZE U, WANG P, HIRATA RK, LI Y, BYERS PH, RUSSELL DW, Mol Ther 16 (2008) 187. DOI: 10.1038/sj.mt.6300339. — 30. IVKOVIĆ A, PASCHERA, HUDETZ D, JELIĆ M, HAŠPL M, WINDHAGER R, PEČINA M, Acta Ortho Traum Checosl 73 (2006) 115.

D. Primorac

University of Split, School of Medicine, Spinčićeva 1, 21000 Split, Croatia
e-mail: draganprimorac2@gmail.com

OSTEOGENESIS IMPERFECTA – VIŠE-SUSTAVNA, DOŽIVOTNA BOLESTI I NJEN UTJECAJ NA OBITELJ

S A Ž E T A K

Osteogenesis imperfecta (OI) ili bolest krhkih kostiju najčešća je nasljedna bolest koja primarno pogađa koštano tkivo. Prema dostupnim podacima u Hrvatskoj od OI boluje oko 400 pojedinaca, a procijenjuje se da još dvostruko toliko ljudi boluje od blažeg oblika bolesti, te stoga niti dijagnoza nije postavljena. Kako se radi o relativno malom broju oboljelih, većina liječnika ima ograničeno iskustvo u liječenju ovih bolesnika, bilo da se radi o djeci ili o odraslima. U podlozi OI nalazi se abnormalna sinteza kolagena, koji je glavni protein izvanstaničnog matriksa mnogih tkiva. Iako kliničkom slikom dominiraju prijelomi, zahvaćena su i nemineralizirana tkiva te se promijene očituju na a koži, tetivama, bjeloočnicama, zubima i krvnim žilama. Klinička slika je vrlo heterogena te se mogu pojaviti znakovi i simptomi kao što su plavkasta obojenost bjeloočnica, gluhoća, poremećaj u razvoju zuba, povećan opseg pokreta u zglobovima (hiperlaksitet) i elasticitet kože, sklonost hernijama (kilama), krhkost kapilara, aneurizme, mlohavost srčanih zalistaka i dr. Iako ne postoji mogućnost izliječenja ovih bolesnika, na raspolaganju nam stoji čitav niz specifičnih terapijskih procedura koje mogu smanjiti bol i komplikacije povezane s osnovnom bolešću, te značajno povećati kvalitetu života bolesnika s OI. Cilj ovog preglednog članka je prikazati molekularnu osnovu bolesti, opisati kliničku sliku te prikazati najosnovnije modalitete ortopedskog liječenja pacijenata s OI.