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Cardiorespiratory complications in patients with osteogenesis imperfecta

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Osteogenesis imperfecta (OI) is a hereditary connective tissue disorder, usually caused by dominant mutations of genes coding for collagen type I alpha chains, COL1A1/A2. Although skeletal manifestations of OI are most readily observable, cardiopulmonary disorders in patients with OI are increasingly recognized as life-threatening but treatable disorders. Unfortunately, the majority of patients with moderate to severe types of OI die from or with cardiopulmonary complications. The lungs and the heart are often unrecognizable and neglected organs in patients with OI. In monitoring of patients with OI, attention is mostly focused on monitoring long bone and spine deformities, and indirectly deformities of the chest wall, which have consequences on the development of lung and the airway diseases. Lung disorder is frequently ignored until breathing problems become severe. An important component in patients with OI is obstructive lung disease, sleep disordered breathing, as well as acute and chronic infection often connected with resultant bronchiectasis. In addition to respiratory complications, some patients with OI have serious cardiovascular problems, including severe mitral valve prolapse, aortic valve insufficiency and dilation of the aorta, which require cardiac surgery. The diagnosis and management of the lung and cardiovascular complications in some patients with OI are quite difficult. In all patients with OI, it is important to recognize and monitor respiratory and cardiovascular manifestations in order to prevent further progression of any complications.

Key words: osteogenesis imperfecta; pulmonary disease; pulmonary function; lung infections; cardiovascular manifestation; prevention

INTRODUCTION

Osteogenesis imperfecta (OI), also known as 'brittle bone disease', is a hereditary disorder of the connective tissue (1, 2) with a heterogeneous clinical phenotype (3). The severity of the disease depends on the effect of a specific mutation. The clinical spectrum of disease phenotypes ranges from perinatal mortality to nearly asymptomatic individuals with occasional fractures and normal stature (4, 5). Although skeletal consequences of OI are well described, less is known about other aspects of the disease, especially the effect of the disease on the appearance and development of respiratory and cardiovascular complications (6, 7).

RESPIRATORY COMPLICATIONS IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

People with moderate and severe OI are more vulnerable to viral and bacterial respiratory infection of upper and lower airways, as well as lung problems, including asthma and pneumonia. Patients with OI have a higher risk of death from respiratory diseases. In fact, respiratory failure is the most common cause of death in people with OI (8-10). A

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British study that investigated the causes of death of patients with OI reports 79 deaths between 1980 and 1995 in a cohort of 1297 patients with OI (4). *McAllion and Paterson* identified respiratory tract infection as the most common cause of death in OI, and found a mean age at death of 6.2 years in severe OI phenotypes and 63.5 years in milder OI phenotypes (8). In a study from Denmark, the authors calculated the risk and cause of death, and median survival time in patients with OI. The median survival time for males with OI was 72.4 years, compared to 81.9 in the reference population. The median survival time for females with OI was 77.4 years, compared to 84.5 years in the reference population. The authors concluded that patients with OI had a higher risk of death from respiratory diseases, gastrointestinal diseases and trauma, and that patients with OI had a higher mortality rate throughout their life compared to the general population (10). Individuals with moderate forms of OI may have near normal life expectancy, but nevertheless, they often require physical aids to walk and to lead normal life (6). Further studies should explore the underlying causes of death, the genotype/phenotype association, and the risk of death related to respiratory complications.

SUBTYPES OF OSTEOGENESIS IMPERFECTA AND RESPIRATORY DISEASES

There are several types of OI and they vary in severity and characteristics. The majority of OI cases (possibly 85-90 percent) are caused by dominant mutation in a gene coding for type 1 collagen COL1A1 and COL1A2 (11). The molecular genetic classification of OI has shown different patterns of inheritance and wide variability of clinical severity (12, 13). In 2009, the Nosology group of the International Society of Skeletal Dysplasias recommended maintaining the Sillence classification as the prototypical and universally accepted form to classify the degree of OI severity (13, 14). *Forlino et al*. categorized OI into five functional metabolic groups, as follows:

a) defects in collagen synthesis, structure or processing;
b) defects in collagen modification;
c) defects in collagen folding and cross-linking;
d) defects in bone mineralization; and
e) defects in osteoblast development with collagen insufficiency (1, 15).

In the past several years, OI has been classified into nine major subtypes based on genetic, radiographic, and clinical characteristics. Types I-IV are caused by dominant mutation in a gene coding for type 1 collagen (2, 16).

Osteogenesis imperfecta type I is the most common and usually the mildest form of OI with normal collagen structure but less than normal amount, with a low risk of development of respiratory complications. Approximately 20 percent of adults with OI type I develop abnormal sideways or front-to-back curvature of the spine (scoliosis or kyphosis) and have a risk of developing restrictive lung diseases (6, 7, 17).

Type II is the most severe type of OI. Infants with type II OI often have underdeveloped lungs and an abnormally small upper chest (thorax), which may result in life-threatening respiratory insufficiency. Type II frequently causes death at birth or shortly after because of respiratory problems. Actually, infants with type II OI usually die within a few hours or days after birth due to respiratory failure related to a small thorax and poor thoracic compliance due to multiple rib fractures (7-9).

Osteogenesis imperfecta type III is the most severe type in children, i.e. those that survive the neonatal period. In OI type III, progressive malformation of various bones may result in short stature, sideways and front-to-back curvature of the spine (scoliosis and kyphosis) (6). In some cases, affected children may develop pulmonary insufficiency and respiratory problems. *Pectus carinatum* characterizes patients with OI type III and alters respiratory muscle coordination, leading to chest wall and rib cage distortions and an inefficient ventilator pattern (1, 6, 18). Development of acute respiratory failure secondary to respiratory tract infection is a common event in patients with OI type III (19, 20). In these patients, development of acute respiratory failure secondary to respiratory tract infection including bronchitis, bronchiolitis, and pneumonia is usually complicated with chronic progressive hypoventilation (7, 18-20).

Individuals with OI type IV have fragile bones that often fracture easily. Fractures are more common before puberty. Affected individuals experience mild to moderate bone malformation and are usually shorter than average. Affected individuals may develop sideways and front-to-back curvature of the spine (scoliosis and kyphosis). OI type IV is characterized by lower alterations in respiratory function, but may have some lung problems such as restrictive lung disease (11).

Types V and VI are similar to types IV and II OI in terms of severity and appearance of respiratory symptoms, however, there is predisposition to hyperplastic callus formation and hyperosteoid bone (2, 21).

Type VII OI is clinically similar to OI types II and IV but has rhizomelia and distinctive feature. Respiratory complications are frequent and often severe (2, 22).

Types VIII-IX OI resemble severe or lethal types II or III in appearance and symptoms, including respiratory complications and death, except for infants having white sclera, severe growth retardation, and extreme skeletal under-mineralization (1, 2, 23).

THE PATHOMECHANISM OF RESPIRATORY COMPLICATIONS IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

Respiratory manifestations in patients with OI are the result of a combination of multiple factors. If the ribs and spine do not develop normally, there may be less space for the lungs to expand, which is often the case in patients with moderate to severe types of OI (1-3). Collagen is also an important building block of connective tissue in the lungs. If the collagen synthesis, structure or function is disturbed, the structure and function of the connective tissue of the lungs are also disturbed, especially structures of the interstitium of the lung (6, 24). In case studies of OI, the pathology of lung hypoplasia is the result of the possible role of mutant collagen. This makes it difficult for affected patients with OI to get enough oxygen through the alveocapillary barrier because of the disturbed biomechanics of breathing (25, 26). Decreased chest volume, chronic infections and inflammation in patients with OI lead to the progression of restrictive pulmonary disorder (20, 26). In addition, patients with OI may have problems on coughing effectively to clear away mucus (4, 5). *Cor pulmonale* is considered a late consequence of pulmonary dysfunction in OI (22). Pulmonary function data in patients with structurally abnormal collagen but without scoliosis, as well as data from both dominant and recessive animal models are needed to delineate the mechanism of pulmonary pathology and development of respiratory complications in patients with OI.

PULMONARY FUNCTION IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

It is known that patients with OI are characterized by disproportional growth affecting predominantly trunk height, collapsing of thoracic vertebrae, more horizontal position of the ribs, and sternal deformities (1-3). In patients with OI type III or IV, the deformed rib cage (i.e. *pectus carinatum*, more horizontal ribs and more compliant rib cage) alters normal action of the intercostal muscles and requires the diaphragm to compensate for their reduced contribution to tidal volume (20, 25). In these patients, inspiratory paradoxical inwards motion of the pulmonary rib cage during spontaneous breathing in supine position is associated with a high level of asynchrony between the three chest wall compartments. Individuals with OI and scoliosis >60° have a striking decline of pulmonary function (25-27). The presence of severe restrictive lung disease with minimal scoliosis raised the possibility that bone-independent pulmonary pathology also contributes substantially to morbidity in those with types III and IV OI (26, 27). *LoMauro et al*. report on reduced forced vital capacity and forced expiratory volume in first second compared to predicted values in both OI types III and IV (20). The ventilation was also lower in OI patients than in controls because of lower tidal volume. The authors showed normal chest wall geometry and function in OI type IV patients. OI type III patients were characterized by reduced angle at the sternum (*pectus carinatum*), paradoxical inspiratory inwards motion of the pulmonary rib cage, significant thoracoabdominal asynchronies, and rib cage distortions in supine position (20). Still, it is not completely clear whether and how these features affect the breathing pattern in OI patients.

RESPIRATORY INFECTIONS IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

Patients with OI breathing problems can develop shortness of breath, tiredness, insomnia and sleep apnea, and it can make the patients more susceptible to respiratory infections (1-3, 8-10, 29). Restrictive pulmonary disorder, a reduction of lung capacity, is common in patients with severe OI or in those with decreased chest volume, chronic bronchitis or asthma, which increases their predisposition to development of lower respiratory infection. Respiratory complications leading to pneumonia or even heart failure represent a significant cause of death in people with types II or III OI (8-10). Difficulties in coughing and expectoration also increase susceptibility to infections in patients with OI. What are all the factors that increase the incidence of infections and whether the function of the immune system is fully preserved in patients with OI remains unknown.

RESPIRATORY COMPLICATIONS IN ADULTS WITH OSTEOGENESIS IMPERFECTA

Some individuals with OI type I are so mildly affected that they are not diagnosed until their teen or adult years. Although often considered a disease with primarily paediatric manifestations, more than 25% of lifetime fractures are reported to occur in adulthood (29). In most cases, individuals with type I OI seem to experience fewer fractures after puberty, when the bones are no longer growing as quickly. Adults with type I OI need to know how the disease can manifest during life and what complications can be expected, including cardiorespiratory complications. General care of adults with OI includes measures to preserve bone density, regular monitoring of hearing and dentition, maintenance of muscle strength through physical therapy, and prevention of the development of cardiorespiratory complications (30). Complications of OI in adulthood from spinal structural abnormalities such as kyphoscoliosis and basilar invagination can cause respiratory insufficiency even in those with OI type I. Adults with OI and small stature, scolio-

sis, or barrel-shaped chest are advised to monitor respiratory function and make pulmonary function test (27). This test should be repeated every 2 years depending on the extent of scoliosis or chest deformity. All patients with OI should be promptly treated for all respiratory infections. Flu shots and pneumococcal vaccines are recommended as well (31).

PREVENTION OF RESPIRATORY COMPLICATIONS IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

In the prevention of serious respiratory complications, the following measures are recommended for patients with OI:

- immediately treat all respiratory infections, even colds and cough;
- immediately treat any difficulties in breathing;
- regularly monitor respiratory functions by pulmonary function testing every year;
- patients with type III or IV OI, or spine curvature, should see a pulmonologist every 1-2 years (32, 33);
- perform breathing exercises and respiratory physical therapy to promote deep breathing. Explain the patient how to exercise safely to develop muscle strength and lung capacity (34);
- children and adults should have spine curvature monitoring (in some cases, surgery may be necessary);
- regularly vaccinate (flu shot and pneumococcal vaccine);
- prohibit cigarette smoking and avoid exposure to second-hand smoke;
- usage of supplemental oxygen and usage of BiPAP (positive pressure breathing device, can help manage pulmonary function) (35);
- treat obstructive lung disease, e.g., asthma. Patients with OI and chronic asthma need additional regular therapy with anti-inflammatory drugs (32-34);
- in cooperation with cardiologist, follow-up development of cardiorespiratory complications such as aortic root dilation and valvular dysfunction. In the assessment of cardiovascular complications, electrocardiogram and echocardiogram should be performed every two years (33); and
- in cooperation with other specialists, get involved in multidisciplinary monitoring of patients with OI (35, 36).

CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

The basic characteristic of OI is deficiency in the production of type I collagen, which is one of the main structural components of connective tissues. Therefore, it is an important component of myocardium and plays a critical role in the structure of blood vessel walls (37, 38). Collagen type I is an important constituent in different parts of the cardiovascular system, including the heart valves, chordae tendinenae, fibrous rings of the heart, interventricular septum, aorta, and the majority of other arteries (39, 40). Collagen fibers in the ventricular myocardium contribute to tensile stiffness and maintain the architecture of the myocytes (39). Valvular regurgitation is a frequently reported cardiovascular disease among patients with OI, but most of the current literature comprises case reports of small case series.

Cross-sectional studies have reported increased aortic root diameter, increased prevalence of diastolic dysfunction and valvulopathies in patients with OI, but most of the included patients were asymptomatic despite cardiovascular pathology (41). The link between connective tissue disorders and cardiovascular pathology is known in disorders including Marfan syndrome, Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome. In all three conditions, patients have vascular fragility, mostly limited to the aorta in Marfan syndrome (42). Taking this in consideration, it would be expected that the prevalence of cardiovascular manifestations in OI is high, but for an irrefutable reason cardiovascular involvement in OI is rare compared with that in Marfan syndrome; however, it can be serious when it occurs (43). The most dramatic and potentially lethal cardiovascular complication is aortic root dissection, although valvular disease and myocardial dysfunction have also been reported (44, 45).

Radunovic et al. conducted a clinical and echocardiographic survey including 99 adults suffering from OI, with the aim to investigate cardiac abnormalities in adult patients with OI. A conclusion based on the study results was that increased left ventricle end diastolic dimension (LVIDd), left ventricular (LV) mass, mitral regurgitation, and aortic regurgitation (AR) were found in adults with OI (46).

A limited number of studies were conducted on children suffering from OI in order to provide evidence that cardiovascular system involvement can occur even without the presence of clinical manifestations. A case-control study was conducted on 24 children suffering from OI and 24 healthy children as a control group in Iran (47). Ejection fraction (EF), shortening fraction (SF), LVIDd, left ventricle end systolic dimension (LVIDs), and left ventricular posterior wall (LVPWd) were determined and the measurements were corrected according to the patient body surface area (BSA). LVIDd, LVPWd, aorta annulus, sinotubular junction, ascending aorta and descending aorta (all parameters corrected for BSA) of the OI patients were significantly higher than those in the control group. Also, Z score calculated for aorta annulus, sinotubular junction, ascending aorta, descending aorta and left ventricle dimensions, which were corrected for BSA, was <2 for all calculated parameters in the control

group, and >2 in patients with OI ranging from 2 to 3.07. In general, Z scores >2 and >2.5 were considered aortic dilation in various studies investigating aortic root dilation (48). Moreover, cardiovascular effects are identifiable in childhood even in mild forms of OI (aortic dilation predominantly), as concluded by *Rush et al.* in their survey of 100 children suffering from OI (49).

The cardiac pathology primarily affects the left-sided heart valves with aortic insufficiency being the most common lesion, followed by mitral regurgitation. *Hortop et al*. report on 6.9% incidence of mitral valve prolapse in their cohort of 109 asymptomatic patients with OI (similar to the 4% to 8% incidence found in normal population) (43).

However, *Radunovic et al*. conducted another study in 2012, which showed that all right ventricle (RV) and pulmonary artery dimensions indexed by BSA were significantly larger in the OI group compared to controls, which means that connective tissue disorder in OI includes not only left ventricle and its structures, but the whole myocardium and both great arteries (50).

Pulmonary insufficiency is the most common cause of demise in type II OI and affects a number of individuals with severe type III OI. Both chest wall pathology and severe kyphoscoliosis associated with vertebral compression can contribute to restrictive lung disease. This may progress to pulmonary hypertension and subsequent *cor pulmonale*, requiring oxygen support. Mitral valve prolapse and aortic dilatation with or without regurgitation have also been reported (22, 27).

More studies are essential for recommending appropriate drug therapy to prevent aortic dilation progress in patients suffering from OI. Some of them have serious cardiovascular problems related to their disease, including severe mitral valve prolapse, aortic valve insufficiency and dilation of the aorta, which require cardiac surgery (51). The friability of the tissues in OI can be hazardous before, during and after the operation. Potential problems related to anaesthesia include the following: difficult intubation because of macroglossia, short neck and neck immobility, fractures from a sphygmomanometer cuff, higher risk of oesophageal tears from a transoesophageal echocardiography probe because of short and immobile neck, epistaxis from nasogastric tube insertion, and dissection of vessels during cannulation. Surgical procedures in OI patients carry a higher risk of bleeding complications, dissection at the cannulation sites, impaired wound healing, and wound dehiscence (52).

The mortality rate in patients with OI who require cardiac surgery is high. Cardiac surgeons recommend that surgical treatment be done gently and surely, having in mind tissue friability, which may decrease mortality after cardiac surgery in OI patients. A multidisciplinary approach with a planned strategy is essential for successful management of patients with OI undergoing cardiac surgery. Heightened awareness among operating theatre and intensive care staff is important for prevention of complications (51, 52).

CONCLUSION

Children and adults with OI more susceptible to developing respiratory complications are those with short stature, scoliosis, kyphosis or both (kyphoscoliosis), chest or rib cage deformities such as *pectus carinatum* or *pectus excavatum*, and those with a sedentary lifestyle.

The rule is that the more severe types of OI are more susceptible to lung or breathing problems. Breathing problems can lead to shortness of breath, tiredness, insomnia, sleep apnoea, and make the patient more susceptible to infections such as pneumonia. Restrictive pulmonary disorder, a reduction of lung capacity, is common in people with severe OI or anyone who has a decreased chest volume. Patients with OI have an increased risk of heart disease, and actually may have an increased risk of developing valvular heart diseases and aortic root dilation in particular. Cardiorespiratory complications leading to pneumonia or heart failure represent a significant cause of death for people with OI type II or III. Regular control and prevention of the development of cardiorespiratory complications is an imperative in the management and treatment of patients with OI.

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SAŽETAK

Kardiorespiracijske komplikacije u bolesnika s osteogenesis imperfecta

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Osteogenesis imperfecta (OI) je nasljedna bolest vezivnog tkiva koja je najčešće uzrokovana dominantnim mutacijama gena koji kodiraju alfa lance kolagena tip I, COL1A1/A2. Iako se su skeletne manifestacije najuočljivije, srčanoplućne bolesti u bolesnika s OI sve se više prepoznaju kao za život opasne bolesti koje se mogu liječiti. Nažalost, većina bolesnika s umjerenim do teškim tipovima OI umire zbog srčanoplućnih komplikacija ili s njima. Pluća i srce često ostaju neprepoznati i zanemareni organi u bolesnika s OI. U praćenju bolesnika s OI pozornost je uglavnom usredotočena na praćenje deformiteta dugih kostiju i kralježnice te neizravno na deformitete stijenke prsnog koša koji utječu na razvoj plućnih bolesti i bolesti dišnih putova. Plućni poremećaj često se zanemaruje sve dok problemi s disanjem ne postanu doista teški. U bolesnika s OI važna sastavnica je opstruktivna bolest pluća, poremećaj disanja u snu te akutna i kronična infekcija koja je često povezana s nastankom bronhiektazija. Uz dišne komplikacije neki bolesnici s OI imaju ozbiljne srčanožilne probleme uključujući težak prolaps mitralnog zaliska, insuficijenciju aortnog zaliska i dilataciju aorte, što zahtijeva operaciju srca. Dijagnostika i zbrinjavanje plućnih i srčanožilnih komplikacija prilično je teško u nekih bolesnika s OI. Kod svih bolesnika s OI važno je prepoznati i pratiti dišne i srčanožilne manifestacije kako bi se spriječilo daljnje napredovanje komplikacija.

Ključne riječi: osteogenesis imperfecta; plućna bolest; plućna funkcija; plućne infekcije; srčanožilne manifestacije; prevencija