

## Cardiovascular Involvement in Children with Osteogenesis Imperfecta

Hamdollah Karamifar, MD; Homa Ilkhanipoor\*, MD; Gholamhossein Ajami, MD; Zohreh Karamizadeh, MD;  
Gholamhossein Amirhakimi, MD; Ali-Mohammad Shakiba, MD

Department of Pediatrics, Namazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

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### Abstract

**Objective:** Osteogenesis imperfecta is a hereditary disease resulting from mutation in type I procollagen genes. One of the extra skeletal manifestations of this disease is cardiac involvement. The prevalence of cardiac involvement is still unknown in the children with osteogenesis imperfecta. The present study aimed to investigate the prevalence of cardiovascular abnormalities in these patients.

**Methods:** 24 children with osteogenesis imperfecta and 24 normal children who were matched with the patients regarding sex and age were studied. In both groups, standard echocardiography was performed, and heart valves were investigated. Dimensions of left ventricle, aorta annulus, sinotubular junction, ascending and descending aorta were measured and compared between the two groups.

**Findings:** The results revealed no significant difference between the two groups regarding age, sex, ejection fraction, shortening fraction, mean of aorta annulus, sinotubular junction, ascending and descending aorta, but after correction based on the body surface area, dimensions of aorta annulus, sinotubular junction, ascending and descending aorta in the patients were significantly higher than those in the control group ( $P < 0.05$ ). Two (8.3%) patients had aortic insufficiency and five (20%) patients had tricuspid regurgitation, three of whom had gradient  $> 25$  mmHg and one patient had pulmonary insufficiency with indirect evidence of pulmonary hypertension. According to Z scores of aorta annulus, sinotubular junction and ascending aorta, 5, 3, and 1 out of 24 patients had Z scores  $> 2$  respectively.

**Conclusion:** The prevalence of valvular heart diseases and aortic root dilation was higher in children with osteogenesis imperfecta. In conclusion, cardiovascular investigation is recommended in these children.

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**Key Words:** Osteogenesis Imperfecta; Cardiovascular Abnormalities; Heart Valve Diseases; Echocardiography

### Introduction

Osteogenesis imperfecta or brittle bone disease is the most prevalent cause of congenital osteoporosis<sup>[1]</sup>. Osteogenesis imperfecta is a rare autosomally inherited disorder which involves the connective tissue<sup>[2]</sup>. Mutations in type I procollagen genes (Col<sub>1</sub>A<sub>1</sub>, Col<sub>1</sub>A<sub>2</sub>) are the most common pathogenesis of osteogenesis imperfecta.

In addition, clinical manifestations of osteogenesis imperfecta are bone fragility, blue sclera, conductive hearing loss, short stature, and dental abnormalities. Bone fragility in osteogenesis imperfecta leads to pathologic fracture and, eventually, deformities in such patients<sup>[1]</sup>.

Overall, osteogenesis imperfecta has a broad spectrum of clinical severity. According to the severity of the symptoms, some classifications are

\* Corresponding Author;

Address: Namazee Hospital, Pediatrics Division, Shiraz, Iran

E-mail: h\_ilkhani66@yahoo.com

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widely used. For instance, osteogenesis imperfecta type II is lethal prenatal type, while type I is a mild form of osteogenesis imperfecta<sup>[2]</sup>. The major treatment for this disorder is antiresorptive therapy, such as pamidronate<sup>[3]</sup>.

Similar to other connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, osteogenesis imperfecta has also extra skeletal manifestations<sup>[4]</sup>. In some studies, cardiovascular involvement is also reported in osteogenesis imperfecta. Of course, most of the studies conducted on the issue have focused on the adults suffering from osteogenesis imperfecta and reported various results<sup>[5-11]</sup>. The most common cardiovascular abnormalities in such patients were aortic root dilatation and heart valves insufficiency.

Several studies have also been performed on adults suffering from osteogenesis imperfecta who were in need of heart valve replacement, particularly aortic valve. Some cases of mitral insufficiency have been reported, as well<sup>[12-22]</sup>.

Nevertheless, a limited number of studies have been conducted on the children suffering from osteogenesis imperfecta. Considering the cardiovascular involvement as one of the major extra skeletal manifestations of the disease, and due to limited investigations on the prevalence of cardiovascular abnormalities in children with osteogenesis imperfecta, the present study aimed to investigate the rate of cardiovascular abnormalities among the children with osteogenesis imperfecta.

## **Subjects and Methods**

The present case-control study was conducted on 24 children suffering from osteogenesis imperfecta who were referred to the pediatric endocrinology ward of Namazi hospital, Shiraz, Iran for receiving intravenous pamidronate during 9 months. The history of all the children was obtained and they underwent physical examination. In addition, information with respect to age, sex, number of fractures, and time of the incidence of the first fracture, were recorded. Height, weight, and body surface area (BSA) were also measured. Standard 2-dimensional, M. mode

color Doppler and pulsed Doppler echocardiography was done by a pediatric cardiologist using echo machine Vivid 3 ( Vingamed Technology). Ejection fraction (EF), shortening fraction (SF), left ventricle end diastolic dimension (LVIDd), left Ventricle end systolic dimension (LVIDs), and left ventricular posterior wall (LVPWd) were determined and the measurements were corrected for the patients based on the BSA. Mitral valve, tricuspid valve, and pulmonary valve were examined as well. In the echocardiography, aorta annulus, sinotubular junction, ascending aorta and descending aorta diameters were measured and corrected according to the patients' BSA.

In this study, Z score was calculated for aorta annulus, sinotubular junction, ascending aorta and left ventricle dimensions with the help of parameterz.blogspot.com.

In order to select the control group, 24 children who were referred to the pediatric emergency room of Namazee hospital, Shiraz, Iran due to outpatient problems, such as upper respiratory tract infection, were voluntarily enrolled in the study as controls. They were matched with the patients regarding age and sex. In the case that they had no special problems, they were entered into the control group. It should be noted that these patients did not have the history of cardiovascular diseases, chronic pulmonary diseases such as asthma, and other chronic or major organ diseases. All of the individuals were examined by a pediatrician. As these children did not have any significant problem and were afebrile, enrolled in the study.

For 24 normal children, all the parameters were measured by echocardiography and were used as control group.

All the patients' data were recorded in the related forms and analyzed using the SPSS statistical software. Mean and standard deviation were computed for the dependent variables. Besides, t-test and chi-square test were used in order to compare the two groups.

## **Findings**

The present study was conducted on 24 children with osteogenesis imperfecta and 24 normal

**Table 1:** Demographic data of patients with osteogenesis imperfecta and control subjects

Parameter	OI Group (n=24) Mean (SD)	Control Group (n=24) Mean (SD)	P. value
Age (month)	58.33 (42.80)	57.39 (42.54)	0.9
Weight (kg)	12.77 (5.46)	17.4 (8.90)	0.05
Height (cm)	87.20 (19.56)	100.62 (24.23)	0.04
Body Surface area (m <sup>2</sup> )	0.54 (0.17)	0.68 (0.25)	0.04

OI: Osteogenesis Imperfecta

children as control group. The demographic characteristics of the case and control group are presented in Table 1. Male to female ration in osteogenesis imperfect and control group was 13.1 and 15.9, respectively. According to the results, no significant difference was observed between the two groups regarding sex, age and weight ( $P>0.05$ ).

The results revealed significant difference between the two groups regarding height and BSA. The BSA and height of the osteogenesis imperfecta patients were significantly less than that of the control group ( $P<0.05$ ). The patients age of beginning of the fractures was varied from birth to 24 months with a median age of 2.25 months. The number of fractures varies between 2-15 fractures with median of 5.

Furthermore, mean EF was  $71.37\pm 6.73\%$  and  $73.75\pm 9.52\%$  in the case and the control group, respectively and the difference between the two groups was not statistically significant ( $P>0.05$ ). In addition, the amount of SF was  $39.08\pm 5.81\%$  in the patients group, while  $43.33\pm 10.19\%$  in the control group and no significant difference was observed between the two groups.

The difference between mean LVIDd, LVIDS and LVPWd in two groups were not statistically significant ( $P>0.05$ ), but after adjustment based on BSA the study findings revealed significant difference between the two study groups regarding mean LVIDd/BSA, and LVPWd/BSA

( $P<0.05$ ) (Table 2). The difference between mean aorta annulus, sinotubular junction, ascending aorta and descending aorta dimensions in patients and control group were not statistically significant ( $P>0.05$ ). However, after adjustment based on BSA, aorta annulus/BSA, sinotubular junction based on BSA, ascending aorta based on BSA and descending aorta based on BSA of the osteogenesis imperfecta patients were significantly higher than that of the control group ( $P<0.05$ ) (Table 3). Z score was calculated for aorta annulus, sinotubular junction, ascending aorta and left ventricle dimensions with the help of [www.parameterz.blogspot.com](http://www.parameterz.blogspot.com).

Calculation of Z score for aorta annulus showed that none of the control subjects had Z score  $>2$ . However, among the patients with osteogenesis imperfecta, 2 (8.3%) patients had 2-2.5 Z scores and 3 (12.2%) patients had Z score  $>2.5$  ranging from 2.62 to 3.07. Regarding sinotubular junction, none of the control subjects had Z score  $>2$ . However, one (4.1%) patient had Z score between 2-2.5 and Z scores of two (8.3%) patients were 2.84 and 3.01, respectively. Considering ascending aorta, one (4.1%) patient with osteogenesis imperfecta had Z score  $>2.5$ . Concerning LVPWd Z score, 4 (16.6%) patients in the osteogenesis imperfecta group had Z score  $>2.5$ .

Among 24 children with osteogenesis imperfecta one (4.1%) patient simultaneously suffered from both patent foramen ovale (PFO)

**Table 2:** LVPWd and LVIDd in patients with osteogenesis imperfecta and control subjects, and measurements adjusted for BSA

Parameter	Osteogenesis Imperfecta Group (n= 24)	Control Group (n=24)	P. value
LVPWd (cm)	0.55 (0.18)	0.56 (0.21)	1
LVPWd/BSA (cm/m <sup>2</sup> )	1.08 (0.38)	0.85 (0.26)	0.02
LVIDd (cm)	2.74 (0.55)	2.22 (0.66)	0.3
LVIDd/BSA (cm/m <sup>2</sup> )	5.34 (1.17)	4.64 (1.12)	0.04

LVPWd: Left ventricle post wall dimension; LVIDd: Left ventricle end diastolic dimension; BSA: body surface area

**Table 3:** Aortic dimensions at aorta annulus, sinotubular junction, ascending aorta and descending aorta and corrected values for BSA in osteogenesis imperfecta and control groups

Parameter	Osteogenesis Imperfecta Group (n= 24)	Control Group (n=24)	P. value
Aorta annulus (cm)	1.25 (0.35)	1.21 (0.36)	0.6
Aorta annulus/BSA (cm/m <sup>2</sup> )	2.38 (0.41)	1.84 (0.37)	<0.01
Sinotubular junction (cm)	1.27 (0.37)	1.36 (0.40)	0.5
Sinotubular junction/BSA (cm/m <sup>2</sup> )	2.41 (0.51)	2.07 (0.44)	0.01
Ascending aorta (cm)	1.30 (0.31)	1.17 (0.36)	0.2
Ascending aorta/BSA (cm/m <sup>2</sup> )	2.53 (0.69)	1.77 (0.27)	<0.01
Descending aorta (cm)	0.89 (0.20)	0.86 (0.25)	0.6
Descending aorta/BSA (cm/m <sup>2</sup> )	1.74 (0.41)	1.32 (0.21)	<0.01

BSA: body surface area

and patent ductus arteriosus (PDA). Also, one child suffered from PFO alone. Furthermore, 2 (8.3%) patients had aortic valve insufficiency in echocardiography; such a way that one patient had trivial AI and the other had mild AI. Besides, one patient suffered from pulmonary valve insufficiency and had indirect evidence of pulmonary hypertension. Moreover, 5 (20%) patients suffered from tricuspid regurgitation with gradients of (15-44.8) mm Hg.

Finally, the study results revealed no significant relationship between cardiac abnormalities and the patients' age, sex, number of fractures, and number of times of receiving pamidronate.

## Discussion

Osteogenesis imperfecta is a genetic disease which occurs due to deficiency in production of type I collagen. Since type I collagen is one of the main structural components of connective tissues, this disease can have various extra skeletal clinical manifestations<sup>[23]</sup>. In general, type I collagen is the most important structural component of myocardium<sup>[24]</sup>. Moreover, it plays a critical role in the structure of blood vessels walls<sup>[25,26]</sup>. Various studies have proved that mutations in osteogenesis imperfecta severely affect the amount and quality of tissue collagen<sup>[27]</sup>. Therefore, collagen disorders in osteogenesis imperfecta patients are responsible for valvular heart diseases as well as aortic disorders. The prevalence of cardiovascular abnormalities in

osteogenesis imperfecta is still unknown and a limited number of studies have been conducted on the children in this regard.

In the present study accompaniment of congenital heart defects such as PFO and PDA with osteogenesis imperfecta seems an incidental phenomenon. In some cases, the simultaneous incidence of congenital heart diseases, such as Ebstein's anomaly, and osteogenesis imperfecta has also been reported<sup>[8]</sup>.

In general, various methods are used for assessment of cardiac structures obtained through M-mode echocardiography. The absolute values of these measures are employed for adults. Regarding the children, on the other hand, different methods, including computation of Z score, observed to expected values ratio, and investigation of the measures based on the body surface area, are utilized<sup>[28]</sup>.

In general, Z scores >2 and >2.5 have been considered as aortic dilation in various studies investigating aortic root dilation<sup>[28]</sup>. In Radunovic's study the same result was reported. Radunovic et al performed a study in 2010 and showed that all aortic parameters after adjustment according to BSA were significantly higher among the patients compared to the control group. In addition, 10.1% of the patients had mild and 10.1% moderate AR, respectively and the difference in the prevalence rate might be due to the study sample size and the fact that the study was conducted on the adult population<sup>[10]</sup>.

In the case reports published regarding adults suffering from osteogenesis imperfecta, several cases of osteogenesis imperfecta patients have been reported who had AI and, as time went by,

had to undergo aortic valve replacement. Byra et al reported five patients with osteogenesis imperfecta and aortic dissection<sup>[29]</sup>.

In the present study, five (20%) patients had TR, three of whom had a gradient more than 25 mmHg. Besides, one patient had PI and indirect evidence of pulmonary hypertension which might have been due to the chest deformities resulting from recurrent fractures in such patients. In another study conducted on the adults with osteogenesis imperfecta by Radunovic et al in 2012, the rate of right ventricle and pulmonary artery dimensions in the osteogenesis imperfecta patients were higher than in the control group<sup>[12]</sup>. Thus, one can conclude that although several studies have reported involvement of the left side of the heart and the aortic root as the most prevalent abnormalities accompanied by osteogenesis imperfecta, considering the widespread nature of the disease, right side of the heart can be involved, too.

Some drugs such as beta blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were suggested for preventing aortic dilation progression in patients suffering from Marfan syndrome<sup>[28]</sup>, but in patients with osteogenesis imperfecta more studies are necessary.

We will follow our patients who suffer from aortic root dilation or valvular insufficiency to evaluate progression of these abnormalities and to investigate probable medical treatments. Up to now, a limited number of studies have been performed on the children suffering from osteogenesis imperfecta. For instance, in the study conducted by Veteru et al, aortic root dilatation and congenital cardiac malformations, such as AS, ASD, and Fallot tetralogy, were observed in the children with osteogenesis imperfecta<sup>[30]</sup>. However, in contrast to other connective tissue disorders, such as Marfan syndrome, the prevalence of cardiovascular abnormalities among the osteogenesis imperfecta patients is still unknown<sup>[4]</sup>.

One of the limitations of the present study was its small sample size. In fact, further studies with larger sample size are required in order to determine the actual prevalence of cardiovascular abnormalities among the children suffering from osteogenesis imperfecta.

## Conclusion

Considering the fact that deficiency in type I collagen is the cause of osteogenesis imperfecta and cardiovascular system involvement is one of the manifestations of the disease which can even occur without the presence of clinical manifestations, all osteogenesis imperfecta children are recommended to be examined regarding cardiovascular involvement. Moreover, since echocardiography is a safe, non-invasive imaging method, it is recommended for the children suffering from osteogenesis imperfecta.

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**Conflict of Interest:** None

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