



ORIGINAL ARTICLE

# Cardiological assessment of a cohort of Egyptian patients with osteogenesis imperfecta type III



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## KEYWORDS

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Ventricular function;  
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**Abstract** *Background:* Osteogenesis imperfecta is a genetic disorder of bones, which has different types. Type III is characterized by recurrent fractures, progressive bone deformities. Cardiac manifestation is one of the important extraskelatal manifestations.

*Aim of the study:* To assess the ECHO cardiographic findings in Egyptian osteogenesis imperfecta patients type III (OI III).

*Patients and methods:* This retrospective study included 35 OI III patients. Their age ranged from 2 months to 18 years with a mean of  $6.34 \pm 4.85$ . Standard echocardiography was performed, and heart valves were examined. The dimensions of the left ventricle, and ejection fraction were measured.

*Results:* Abnormal ECHO findings were found in 8 patients (22.9%). Atrial septal defect (ASD), and patent ductus arteriosus (PDA) were the commonest cardiac findings with 5.7% each. Trivial tricuspid regurgitation was found in 9 patients, this was considered normal finding. There was no significant difference in ECHO findings between males and females with OI III.

*Conclusion and recommendation:* The presence of cardiac abnormalities is documented in OI patients whether congenital or valvular, and so ECHO cardiography should be routine in all patients with OI.

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## 1. Introduction

Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by increased risk of fractures with or without trauma. Other characteristic features include blue sclera, triangular face, hearing loss more observed in old patients [1].

Osteogenesis imperfecta was divided into several types according to the pattern of inheritance, and phenotype. In 1979, Silence et al. proposed a phenotypic classification system for OI with four types based on severity: type I mild non-deforming, type II perinatal lethal, type III severely deforming, and type IV moderately deforming [2]. Another classification was proposed in 2010 dividing OI into 5 types depending on clinical and molecular classification [3]. OI is classified into 11 types to date, on the basis of their clinical symptoms and genetic components [4].

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Up to 90% of individuals with OI are heterozygous for mutations in the COL1A1 and COL1A2 genes. Mutations in several different genes also were identified as a cause of OI including CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, SERPINH1, SP7, WNT1, BMP1, TMEM38B, IFITM5 gene, and PLS3 genes [5]. Decreased synthesis of normal collagen to 50% due to one null allele of COL1A1 gene mutations results in mild type I OI while mutations of procollagen chains genes have more deleterious phenotypic consequences (types II, III and IV OI) [6].

Several extraskeletal manifestations are present including cardiac, renal, dental, and ocular manifestations [7]. A limited number of studies have been conducted on the children with OI to assess the prevalence of cardiovascular abnormalities [8].

The non-skeletal manifestations of OI in the respiratory and cardiovascular systems are the main cause of mortality and morbidity in OI which may be due to skeletal changes [9].

Cardiovascular findings which had been reported previously include valvular (aortic, and mitral) insufficiency, aortic root dilation, atrial septal defects and septal and posterior left ventricular wall thickening, and impairment of diastolic function [7,10–15].

## 2. Subjects and methods

This retrospective study included 35 infants and children diagnosed with osteogenesis imperfecta type III (OI III) according to Sillence classification [2]. The patients were following up at the Genetics Unit, Children's Hospital, Faculty of Medicine, Ain Shams University, Cairo, Egypt. By revising the data recorded in the files, detailed full history with special emphasis on age, sex, symptoms of cardiac affection was reviewed.

A standard two-dimensional, M-mode, color flow, continuous wave and pulsed wave (PW) Doppler echocardiography examinations were performed for all patients using the segmental sequential approach.

### 2.1. Statistical methodology

Analysis of data was performed using standard computer program statistical package for social sciences (SPSS) 15 for windows (SPSS Incorporation, USA).  $P < 0.05$  was considered significant.

## 3. Results

This study included 35 OI III infants and children, they were 18 males (51.4%) and 17 females (48.6%). Their age ranged from 2 months to 18 years with a mean of  $6.34 \pm 4.85$ . Parental consanguinity was positive in 65.6% of patients.

ECHO cardiography results showed that 27 patients (77.1%) had normal cardiac function, and 8 patients (22.9%) had abnormal ECHO findings (Table 1). Atrial septal defect (ASD), and patent ductus arteriosus (PDA) were the commonest cardiac findings with 5.7% each. Trivial tricuspid regurge (TR) was found in 9 patients but it was considered normal finding.

Estimations of ventricular dimensions, and ejection fraction were done (Table 2).

Cardiac murmur was evident during examination in (5/35) 14.3% of patients, those patients had ASD, ventricular septal defect (VSD), or PDA which were confirmed by ECHO, while

**Table 1** ECHO cardiographic findings in OI III patients.

	Frequency	Percent
Normal	27	77.1
Abnormal		
AR dilatation	1	2.9
ASD	2	5.7
MVP	1	2.9
MVP, MR, AVP	1	2.9
PDA	2	5.7
VSD	1	2.9
Total	8	22.9
Total	35	100.0

ASD: atrial septal defect, PDA: patent ductus arteriosus, AR: aortic root, MVP: mitral valve prolapse, MR: mitral regurge, AVP: aortic valve prolapse, VSD: ventricular septal defect.

patients with valvular affection were detected by ECHO only with no cardiac murmurs or clinical manifestations.

A female patient who had ASD was maintained on treatment for control of heart failure in the form of lasix and lanoxin. Later the patient died of cardiac complications at the age of 3 years. The cardiac condition in the other patients with abnormal findings was stable and did not necessitate specific treatment.

There was no significant difference in ECHO findings between males and females with OI III as shown in Table 3.

## 4. Discussion

OI preferentially affects the left-sided heart valves, leading to aortic and mitral regurgitation. The valvular insufficiency in patients with osteogenesis imperfecta results from an underlying defect in connective tissue formation [8], however aortic root dilation is the most common cardiovascular manifestation [15].

In this study, abnormal ECHO findings were detected in 22.9% (8/35) of patients with OI III, from which 14.3% (5/35) were congenital heart disease. This finding was higher than what was reported in a previous study done by Veter who reported congenital heart disease in 6.9% (4/58) of patients with osteogenesis imperfecta of any type, and 8% (2/25) OI III patients had congenital heart disease [7].

The prevalence of congenital heart in this study is much higher than that in normal population which differs greatly from study to study, it ranged from 4/1,000 to 50/1,000 live births [16].

In this study ASD, PDA were the commonest congenital heart diseases detected followed by VSD. ASD was reported previously in OI III patients, also other types of congenital heart were also reported in different types of OI including Fallot tetralogy, congenital aortic stenosis, also increased septal (40%) and posterior left ventricular wall thickening (68%) [7].

In this study there was valvular affection in 8.6% (3/35) of patients, which represents 37.5% of the abnormal cardiac findings in OI III patients. Of which mitral regurge (MR), mitral valve prolapse (MVP), and dilated aortic root were documented once each. Valvular dysfunction was previously detected in 3.7% (4/109) of patients (aortic regurgitation in two, aortic stenosis, mitral valve prolapse in one each) [10]. Both studies' results were comparable.

**Table 2** Estimation of different cardiac functions.

	LVEDD	LVPWTD	LVESD	IVSD	LAD	AR	ACS	EF	PP	FS
Mean	33.14	4.83	18.80	10.00	27.33	19.25	13.00	68.43	24.25	51.00
Median	35.00	4.80	20.00	5.00	25.50	19.00	13.00	69.00	24.00	47.00
SD	4.981	.898	2.683	8.266	15.946	1.258	.816	8.203	2.217	14.422
Range	14	2	6	19	48	3	2	21	5	28
Minimum	23	4	15	4	6	18	12	59	22	39
Maximum	37	6	21	23	54	21	14	80	27	67

LVEDD: left ventricular end diastolic diameter, LVPWTD: left ventricular posterior wall thickness in diastole, LVESD: left ventricular end systolic diameter, IVSD: interventricular septum in diastole, LAD: left atrial diameter, AR: aortic root, EF: ejection fraction, PP: pulmonary pressure, FS: fractional shortening.

**Table 3** Correlation between sex of the patient and ECHO findings.

ECHO		AR dilatation	ASD	MVP	MVP, MR, AVP	Normal	PDA	VSD	Total	P
Sex	Female	0	2	1	1	11	1	1	17	0.33
	Male	1	0	0	0	16	1	0	18	
	Total	1	2	1	1	27	2	1	35	

ASD: atrial septal defect, PDA: patent ductus arteriosus, AR: aortic root, MVP: mitral valve prolapse, MR: mitral regurge, AVP: aortic valve prolapse, VSD: ventricular septal defect.

Aortic root dilatation was reported in 2.9% (1/35) of patients. The percent of aortic root dilatation was different in different studies; it ranged between 12.1% [10] and 28% [7]. The variation in the percentage of affection between different studies may be related to age difference, being higher in Vetter et al., study [7]. Also its extent was mild nonprogressive and may be not related to age, and it was segregated within certain families [10].

Mitral valve prolapse represents (2/35) 5.7% either alone (1/35) or associated with mitral regurge (1/35). It was reported in Hortop et al., study to be 6.9% which was similar to adult population [10].

Patients with OI III had right ventricular (RV) dimensions and pulmonary artery (PA) which were significantly larger compared to patients with OI I, IV and controls [17]. In this study RV and PA dimensions were within the normal range.

Also, the study results revealed no significant difference between cardiac abnormalities and the patients' sex, which is the same finding reported by Karamifar et al. [8].

Parental consanguinity was present in 65.6% of the patients which is high and cannot be explained by the high consanguinity rate in Egypt [18]. But it supports the findings that OI III is mostly an autosomal recessive disease.

## 5. Conclusion and recommendations

The presence of cardiac abnormalities is documented in OI patients whether congenital or valvular and it needs further studies to detect if it is related to specific type or genetic abnormalities.

## Conflict of interest

All authors declare that they have no conflict of interest.

## References

- [1] Marini JC, Forlino A, Cabral WA, Barnes AM, San Antonio JD, Milgrom S, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum Mutat* 2007 Mar;28(3):209–21.
- [2] Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979;16(2):101–16, 10.1136.
- [3] Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A* 2014;164A(6):1470–81.
- [4] Womack J. Osteogenesis imperfecta types I–XI: implications for the neonatal nurse. *Adv Neonatal Care* 2014;14(5):309–15, 316–7.
- [5] Valadares ER, Carneiro TB, Santos PM, Oliveira AC, Zabel B. What is new in genetics and osteogenesis imperfecta classification? *J Pediatr (Rio J)* 2014;90(6):536–41.
- [6] Gajko-Galicka A. Mutations in type I collagen genes resulting in osteogenesis imperfecta in humans. *Acta Biochim Pol* 2002;49(2):433–41.
- [7] Vetter U, Maierhofer B, Müller M, Lang D, Teller WM, Brenner R, et al. Osteogenesis imperfecta in childhood: cardiac and renal manifestations. *Eur J Pediatr* 1989;149(3):184–7.
- [8] Karamifar H, Ilkhanipoor H, Ajami G, Karamizadeh Z, Amirhakimi G, Shakiba AM. Cardiovascular involvement in children with osteogenesis imperfecta. *Iran J Pediatr* 2013;23(5):513–8.
- [9] Thiele F, Cohrs CM, Flor A, Lisse TS, Przemeczek GK, Horsch M, et al. Cardiopulmonary dysfunction in the Osteogenesis imperfecta mouse model *Aga2* and human patients are caused by bone-independent mechanisms. *Hum Mol Genet* 2012 Aug 15;21(16):3535–45.
- [10] Hortop J, Tsipouras P, Hanley JA, Maron BJ, Shapiro JR. Cardiovascular involvement in osteogenesis imperfecta. *Circulation* 1986;73:54–61.
- [11] Wong RS, Follis FM, Shively BK, Wernly JA. Osteogenesis imperfecta and cardiovascular diseases. *Ann Thorac Surg* 1995;60(5):1439–43.

- [12] Zegdi R, D'Attellis N, Fornes P, Fuzellier JF, Carteaux JP, Fabiani JN, et al. Aortic valve surgery in osteogenesis imperfecta: report of two cases and review of the literature. *J Heart Valve Dis* 1998;7:510–4.
- [13] Ohuchi S, Koizumi J, Kin H, Ohsawa S, Izumoto H, Ishihara K, et al. Valvular heart surgery in osteogenesis imperfecta. *Kyobu Geka* 2002;55(12):1011–3.
- [14] Migliaccio S, Barbaro G, Fornari R, Di Lorenzo G, Celli M, Lubrano C, et al. Impairment of diastolic function in adult patients affected by osteogenesis imperfecta clinically asymptomatic for cardiac disease: casualty or causality? *Int J Cardiol* 2009;131:200–3.
- [15] Bonita RE, Cohen IS, Berko BA. Valvular heart disease in osteogenesis imperfecta: presentation of a case and review of the literature. *Echocardiography* 2010;27(1):69–73.
- [16] Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002 Jun 19;39(12):1890–900.
- [17] Radunovic Z, Wekre LL, Steine K. Right ventricular and pulmonary arterial dimensions in adults with osteogenesis imperfecta. *Am J Cardiol*. 2012 Jun 15;109(12):1807–13.
- [18] Shawky RM, El-Awady YM, Elsayed SM, Hamadan GE. Consanguineous matings among Egyptian population. *Egypt J Med Hum Genet* 2011;12(2):157–63.