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CLINICAL & BASIC RESEARCH

Echocardiographic Evidence of Early Diastolic Dysfunction in Asymptomatic Children with *Osteogenesis Imperfecta*

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أدلة على وجود اختلال مبكر في وظيفة القلب الانبساطية باستخدام تخطيط القلب عند الأطفال المصابين بمرض تكون العظم الناقص

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abstract: ***Objectives:*** Structural and functional cardiovascular abnormalities have been reported in adults with *osteogenesis imperfecta* (OI); however, there is a lack of paediatric literature on this topic. This study aimed to investigate cardiovascular abnormalities in children with OI in comparison to a control group. ***Methods:*** This case-control study was conducted at the Sultan Qaboos University Hospital in Muscat, Oman, between May 2013 and August 2014. Data from eight patients with OI and 24 healthy controls were compared using conventional and tissue Doppler echocardiography (TDE). ***Results:*** The OI group had significantly lower peak early mitral valve flow velocity (P = 0.027), peak a-wave reversal in the pulmonary vein (P = 0.030) and peak early diastolic velocity of the mitral valve and upper septum (P = 0.001 each). The peak late diastolic velocities of the mitral valve (P = 0.002) and the upper septum (P = 0.037) were significantly higher in the OI group; however, the peak early/late diastolic velocity ratios of the mitral valve (P = 0.002) and upper septum (P = 0.001) were significantly lower. Left ventricular dimensions and aortic and pulmonary artery diameters were larger in the OI group when indexed for body surface area. Both groups had normal systolic cardiac function. ***Conclusion:*** Children with OI had normal systolic cardiac function. However, changes in myocardial tissue Doppler velocities were suggestive of early diastolic cardiac dysfunction. They also had increased left ventricular dimensions and greater vessel diameters. These findings indicate the need for early and detailed structural and functional echocardiographic assessment and follow-up of young patients with OI.

Keywords: Children; Osteogenesis Imperfecta; Cardiovascular Abnormalities; Doppler Echocardiography.

الملخص: الهدف: أظهرت الدراسات العلمية وجود اختلالات تكوينية ووظيفية في القلب والأوعية الدموية في البالغين الذين يعانون من مرض تكون العظم الناقص (OI) إلا أن هناك نقص في الدراسات المتعلقة بهذا المرض عند الأطفال. **الطريقة:** هدفت هذه الدراسة إلى التحقق من مدى وجود اختلالات في القلب والأوعية الدموية لدى الأطفال المصابين بهذا المرض بالمقارنة مع مجموعة المراقبة. الطريقة: أجريت هذه الدراسة في مستشفى جامعة السلطان قابوس في مسقط، عمان، بين مايو 2013 وأغسطس 2014 حيث تمت مقارنة بيانات أشعة صدى القلب التكوينية والوظيفية بين 8 مرضى مصابين بمرض تكون العظم الناقص و 24 حالة من مجموعة المراقبة السليمة. **النتائج:** بينت الدراسة أن مرضى تكون العظم الناقص لديهم قياسات أقل بكثير من مجموعة المقارنة لذروة سرعة التدفق المبكر للصمام التاجي ($P = 0.027$) وذروة موجة التراجع في الوريد الرئوي ($P = 0.030$) وذروة السرعة الانبساطية المبكرة للصمام التاجي والحاجز العلوي ($P = 0.001$ لكل منهما). وكانت ذروة السرعة الانبساطية المتأخرة للصمام التاجي ($P = 0.002$) والحاجز العلوي ($P = 0.037$) أعلى بكثير في مجموعة مرضى تكون العظم الناقص؛ ومع ذلك، فإن نسبة الذروة في السرعة الانبساطية المبكرة/المتأخرة للصمام التاجي ($P = 0.002$) والحاجز العلوي ($P = 0.001$) كانت أقل من مجموعة المقارنة بكثير. أيضا كانت أبعاد البطين الأيسر وأقطار الشريان الأبهر و الرئوي أكبر في مجموعة مرضى تكون العظم الناقص عندما تم فهرستها لمساحة سطح الجسم. وبينت الدراسة كذلك أن وظيفة القلب الانقباضية لكلا الفريقين ذات معدل طبيعي. **الخلاصة:** بينت الدراسة أن وظيفة القلب الانقباضية لدى الأطفال المصابين بمرض تكون العظم الناقص ذات معدل طبيعي إلا أنه توجد تغيرات بسيطة توحي بوجود خلل أوّلي في وظائف القلب الانبساطية. كما أنها بينت عن وجود زيادة أبعاد البطين الأيسر وكذلك كبر حجم الأوعية الدموية الرئيسية. هذه النتائج تشير إلى الحاجة إلى التقييم المبكر والمتابعة المستمرة للمرضى الصغار المصابين بمرض تكون العظم الناقص بتخطيط صدى القلب الوظيفي.

مفتاح الكلمات: الأطفال؛ مرض تكون العظم الناقص؛ تشوهات القلب والأوعية الدموية؛ دوبلر صدى القلب.

Advances in Knowledge

- *This study highlights for the first time early changes in the myocardial tissue Doppler velocities of a group of children with osteogenesis imperfecta (OI). These changes suggest the early development of diastolic cardiac dysfunction and preservation of systolic cardiac function in young patients with this genetic disorder.*

Application to Patient Care

- *Cardiovascular assessment of children with OI provides important additional information to support management of this disease.*

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Previously, physicians focused primarily on skeletal malformation and structural and systolic cardiac function; however, with the availability of non-invasive echocardiographic tests, this focus can be extended to diastolic function.

- *Early and newer therapeutic modalities could help treat or modify the progression of OI. This could prevent further deterioration of cardiac function. Early intervention is essential considering the tendency for this group of patients to be limited in their activities and in sports when they reach adulthood.*

Osteogenesis imperfecta (OI) is a group of autosomal disorders of the connective tissues and is commonly caused by mutations in genes encoding the α-1 and α-2 chains of type 1 collagen or proteins involved in the post-translational modification of type 1 collagen.[1] OI is characterised by various skeletal and extraskeletal manifestations.[2] The disease has considerable clinical and biochemical heterogeneity between and within different patients. Common clinical manifestations of this disease are well-known and include blue *sclera*, brittle bones, conductive hearing defects and dental abnormalities.[2]

Tissue Doppler echocardiography (TDE) offers a non-invasive quantitative method of assessing longitudinal systolic and diastolic ventricular performance by measuring velocities directly from the myocardium.[3–5] While a few studies have described cardiovascular involvement among adults with OI, there is very little data available for paediatric patients.[6,7] To the best of the authors' knowledge, this is the first study assessing cardiovascular abnormalities, particularly systolic and diastolic function, in paediatric patients with OI using both conventional and TDE techniques.

Methods

This case-control study was conducted at the Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, between May 2013 and August 2014. All patients diagnosed with OI and followed-up at SQUH during the study period were enrolled in the study. The diagnosis of OI was based on the classification developed by Sillence *et al*.[8] Age- and gender-matched healthy children were included in the study as the control group. The selected controls were either healthy volunteers or had been referred to the clinic because of heart murmurs which were later found to be innocent. A detailed medical history was recorded for each subject, including any existing comorbidities. Anthropometric and physical examinations were performed and heart rates were measured for all participants. Routine complete blood count tests, 12-lead electrocardiography, two-dimensional Doppler echocardiography and pulse TDE were performed on all of the subjects during routine visits to the hospital. Blood pressure was measured in the right arm with an age-appropriate cuff size.

Systolic and diastolic cardiac function was assessed using conventional and TDE techniques. Two-dimensional echocardiography was performed using an ultrasound echocardiography machine (Vivid E9, GE Vingmed Ultrasound AS, Horten, Norway) while the subjects were at rest. Motion (M)-mode, two-dimensional Doppler echocardiography and pulse TDE data were collected by a qualified echocardiographer. The subjects were fully awake during the procedure according to the recommendations of the American Society of Echocardiography.[9]

The left ventricular end systolic (LVISd) and diastolic (LVIDd) dimensions, as well as the septal (IVSd) and left ventricular posterior wall thickness in diastole (LVPWd) were assessed using M-mode from the parasternal long axis view. Subsequently, the shortening fraction (SF) and ejection fraction (EF) were determined.[9] Using the left parasternal long axis view, the aortic *annulus* (AoAn), sinus of Valsalva (SinVals), sinotubular junction (Sintubj) and ascending aorta (AscAo) diameters were measured. From the parasternal high short axis view, diameter measurements of the pulmonary valve *annulus* (PVAn), main pulmonary artery (MPA) and left (LPA) and right (RPA) pulmonary arteries were taken. The early (Em) and late (Am) peak velocities of the mitral valve inflow, deceleration time of the Em wave (DTm) and Am wave duration were measured from the four chamber view with placement of the pulse Doppler sample volume at the tips of the valve leaflets. Isovolumic relaxation time (IVRT) was measured by placing the continuous Doppler sample volume in the left ventricular outflow tract in the three chamber view. Assessment of the right upper pulmonary vein pulse Doppler pattern was taken from a four chamber view to measure the systolic (Spv), diastolic (Dpv) and a-wave reversal peak velocity (Apv) and duration (Apvd). The Spv/Dpv ratio and the mitral valve inflow late velocity duration and a-wave duration ratio of the pulmonary veins (Amd/Apvd) were obtained.

TDE was performed by placing the sample volume at the corner of the mitral *annulus*, the upper part of the interventricular septum and the corner of the tricuspid valve in the four chamber view. In each region, the systolic (S') wave, early diastolic (E') and late diastolic (A') velocities were recorded and the

Em/peak early diastolic velocity of the mitral valve (E'm) ratio was obtained. Global systolic myocardial function was evaluated by EF and SF using M-mode in addition to the peak systolic velocities (S') of the TDE.

In the early stages of diastolic dysfunction, impaired relaxation and passive filling of the left ventricle predominates, resulting in a low Em and E'm, high Am and peak late diastolic velocity of the mitral valve (A'm) and low Em/Am and E'm/A'm ratios.[10] Another reliable indicator of diastolic dysfunction is a high Em/E'm ratio, which is an estimate of the filling pressure of the left ventricle.[11] Assessment of pulmonary hypertension was performed by measuring the maximum velocity of the tricuspid valve regurgitation jet, if present, as well as the pulmonary valve regurgitation peak velocity. The Z score was calculated for AoAn, SinVals, Sintubj, PVAn, MPA, RPA, LPA and left ventricular dimensions.[12] All measurements reported in this study represent the average value of at least three cardiac cycles per subject.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), Version 20.0 (IBM Corp., Chicago, Illinois, USA). All results were expressed as means ± standard deviation. The independent Student's t-test and Mann-Whitney U test were used when appropriate. A multivariate linear regression was used to find the impact of baseline differences between the two groups, including the diagnosis of OI. Differences were considered statistically significant at P <0.050.

This study was approved by the Medical Research & Ethics Committee of the College of Medicine & Health Sciences at Sultan Qaboos University (MREC #672). Informed written consent was obtained from the parents or caregivers of all subjects before inclusion in the study.

Results

A total of eight OI patients with a mean age of 7.3 ± 4.3 years were diagnosed and followed-up at SQUH during the study period. The male-to-female ratio was 3:5. Seven of these patients had OI type III while one had OI type IV. A total of 24 controls with a mean age of 6.9 ± 2.5 years were also included. The male-to-female ratio was 11:13. Both groups were proportionately similar in age and gender; however, there were significant differences in their height, weight and body surface area (BSA) [Table 1].

All of the OI patients had fractures and had been receiving pamidronate infusions every three months as part of their disease management plans. There was no evidence of systemic disease and none of the patients were taking other medications. The OI subjects were asymptomatic from a cardiac point of view and none had mitral or aortic valve regurgitation. None of the OI subjects had systemic hypertension and they were all in sinus rhythm. There was no electrocardiographic evidence of Wolff-Parkinson-White syndrome among any of the patients.

Standard two-dimensional echocardiography measurements and Z scores for both groups are reported in Table 2. Left ventricle and left atrium dimensions, aortic and pulmonary artery diameters and left ventricular systolic function data were not statistically significant between the two groups. However, when the left ventricular dimensions, aortic and pulmonary artery diameters were corrected for BSA, there was a statistically significant difference between the two groups. None of the subjects who had mild tricuspid valve regurgitation showed evidence of pulmonary hypertension (18.6 ± 1.4 mmHg [n = 7] versus 17.4 ± 2.7 mmHg [n = 22]; P = 0.278) and the other subjects did not have echocardiographic evidence of elevated right ventricular pressure from assessment of the septal curvature and pulmonary valve regurgitation jet. Corrected IVRT for heart rate was comparable between the OI and control group (88.1 ± 17.4 ms versus 79.5 ± 11.9 ms; P = 0.125). Calculations of the Z score revealed that there was a statistically significant difference between the OI and the control group regarding aortic and pulmonary artery diameters. Regarding the left ventricular dimensions, the OI group had a larger Z score for the IVSd and LVPWd, but no significant difference was observed for the LVISd and LVIDd Z scores. None of the control subjects had a Z score of >2.

Other conventional and TDE assessment data are summarised in Table 3. There was a statistically significant decrease in the Em velocity for the OI group compared to the controls (84.8 ± 23.4 cm/s versus 103.4 ± 18.4 cm/s; P = 0.027). However, the Am and DTm measurements and Em/Am ratio were similar. A significant difference was observed in the TDE measurements of the lateral mitral valve and upper septum but with a comparable Em/E'm ratio and peak systolic velocity at all the measured sites. TDE measurements at the lateral tricuspid valve were similar between the two groups. Right upper pulmonary vein Doppler velocities and duration showed no statistically significant difference between the two groups with respect to Spv and Dpv peak velocities. However, a significant difference was observed for the Spv/Dpv ratio, peak a-wave reversal and duration. In contrast, there was a comparable Amd/Apvd ratio for the OI and control subjects (1.6 ± 0.5 versus 1.3 ± 0.4; P = 0.136).

Multiple linear regression analysis showed that BSA was a significant predictor for LVIDd, LVISd,

Table 1: Characteristics of children with *osteogenesis imperfecta* in comparison to an age- and gender-matched control group (N = 32)

Characteristic	Mean ± SD		*P* value
	OI group (n = 8)	Control group (n = 24)	
Male-to-female ratio	3:5	11:13	0.692
Age in years	7.3 ± 4.3	6.9 ± 2.5	0.743
Height in cm	87.3 ± 24.9	124.0 ± 14.3	0.001
Weight in kg	15.0 ± 9.9	22.7 ± 7.4	0.025
BSA in m^2	0.60 ± 0.28	0.89 ± 0.19	0.001
Systolic BP in mmHg	100.6 ± 5.0	103.4 ± 6.8	0.324
Diastolic BP in mmHg	57.1 ± 4.0	60.5 ± 5.0	0.136
Heart rate in beats per minute	105.5 ± 22.0	85.9 ± 17.0	0.054
QTc in ms	422.4 ± 11.0	418.4 ± 22.0	0.623
Haemoglobin in g/dL	11.9 ± 1.3	11.7 ± 0.6	0.634
Median haematocrit % (IQR)	0.4 (0.34–0.40)	0.4 (0.35–0.38)	0.717
Age started on pamidronate in months	38.9 ± 29.1	-	-
Duration of pamidronate therapy in months	54.5 ± 60.8	-	-

SD = standard deviation; OI = osteogenesis imperfecta; BSA = body surface area; BP = blood pressure; QTc = QT interval corrected for heart rate; IQR = interquartile range.

Table 2: Echocardiographic measurements and Z scores of children with *osteogenesis imperfecta* in comparison to an age- and gender-matched control group (N = 32)

Measurement/Z score	Mean ± SD		*P* value
	OI group (n = 8)	Control group (n = 24)	
Median LVIDd in mm (IQR)	31.0 (25.5–38.0)	38.0 (33.0–41.0)	0.051
LVIDd/BSA ratio	61.4 ± 13.6	44.1 ± 7.1	0.009
LVIDd Z score	0.7 ± 1.1	0.1 ± 0.8	0.080
LVISd in mm	20.0 ± 5.3	24.3 ± 3.6	0.065
LVISd/BSA ratio	37.4 ± 8.5	27.9 ± 3.9	0.015
LVISd Z score	0.4 ± 1.1	0.2 ± 0.7	0.441
IVSd in mm	6.5 ± 1.3	5.7 ± 1.0	0.151
IVSd/BSA ratio	12.7 ± 4.3	6.7 ± 1.8	0.005
IVSd Z score	1.4 ± 0.8	-0.1 ± 0.9	0.001
Median LVPWd in mm (IQR)	5.0 (5.0–6.5)	5.0 (4.0–5.0)	0.160
LVPWd/BSA ratio	10.7 ± 2.8	5.7 ± 1.6	0.001
LVPWd Z score	1.6 ± 0.3	-0.3 ± 0.8	0.001
EF in %	71.0 ± 4.2	66.4 ± 5.8	0.050
SF in %	39.1 ± 3.1	36.3 ± 4.6	0.068
AoAn in mm	14.8 ± 2.5	15.1 ± 1.8	0.680
AoAn/BSA ratio	28.5 ± 7.8	17.3 ± 2.0	0.005
AoAn Z score	2.9 ± 1.2	0.3 ± 0.5	0.001
SinVals in mm	18.6 ± 2.5	18.9 ± 2.7	0.793
SinVals/BSA ratio	36.6 ± 11.1	21.7 ± 2.6	0.007
SinVals Z score	1.8 ± 1.6	-0.5 ± 8.0	0.001
Sintubj in mm	16.9 ± 2.0	16.6 ± 2.3	0.786
Sintubj/BSA ratio	33.2 ± 10.5	19.1 ± 2.6	0.007
Sintubj Z score	2.4 ± 1.3	0.2 ± 0.7	0.001
AscAo in mm	17.3 ± 3.6	16.9 ± 2.2	0.758
AscAo/BSA ratio	33.5 ± 11.6	19.4 ± 2.4	0.011
AscAo Z score	2.1 ± 2.3	-0.3 ± 1.0	0.001
PVAn in mm	15.4 ± 2.9	16.0 ± 2.8	0.570
PVAn/BSA ratio	29.4 ± 7.2	18.4 ± 2.8	0.003
PVAn Z score	1.6 ± 2.3	-0.7 ± 0.8	0.001
MPA in mm	16.4 ± 1.8	15.3 ± 2.1	0.189
MPA/BSA ratio	32.1 ± 9.6	17.7 ± 3.3	0.003
MPA Z score	1.2 ± 1.1	-1.1 ± 0.8	0.001
LPA in mm	11.5 ± 1.9	11.5 ± 1.1	0.941
LPA/BSA ratio	22.3 ± 6.0	13.5 ± 3.2	0.004
LPA Z score	2.7 ± 0.9	0.9 ± 0.8	0.001
RPA in mm	11.9 ± 3.1	11.3 ± 1.2	0.473
RPA/BSA	22.3 ± 5.0	13.2 ± 2.6	0.001
RPA Z score	2.0 ± 0.7	0.0 ± 0.8	0.001
TVmax in mmHg	18.6 ± 1.4 (7)*	17.4 ± 2.7 (22)*	0.278
LA/AO ratio	1.4 ± 0.2	1.5 ± 0.2	0.315
IVRT in ms	67.5 ± 14.1	67.2 ± 11.2	0.946
Corrected IVRT† in ms	88.1 ± 17.4	79.5 ± 11.9	0.125

SD = standard deviation; OI = osteogenesis imperfecta; LVIDd = left ventricular end diastolic dimension; IQR = interquartile range; BSA = body surface area; LVISd = left ventricular end systolic dimension; IVSd = interventricular septal dimension in diastole; LVPWd = left ventricular posterior wall dimension in diastole; EF = ejection fraction; SF = shortening fraction; AoAn = aortic valve annulus; SinVals = sinus of Valsalva; Sintubj = sinotubular junction; AscAo = ascending aorta; PVAn = pulmonary valve annulus; MPA = main pulmonary artery; LPA = left pulmonary artery; RPA = right pulmonary artery; TVmax = tricuspid valve regurgitation maximum peak velocity; LA/AO = left atrium aortic dimension ratio by M-mode; IVRT = isovolumic relaxation time.

**Number of subjects with mild tricusoid valve regurgitation and for whom TVmax could be measured. †Corrected for heart rate.*

Table 3: Tissue Doppler echocardiographic measurements of children with *osteogenesis imperfecta* in comparison to an age- and gender-matched control group (N = 32)

Measurement	Mean ± SD		*P* value
	OI group (n = 8)	Control group (n = 24)	
Mitral valve			
Em in cm/s	84.8 ± 23.4	103.4 ± 18.4	0.027
Am in cm/s	52.4 ± 20.9	50.9 ± 11.6	0.810
Em/Am ratio	1.8 ± 0.6	2.1 ± 0.4	0.156
Amd in ms	102.1 ± 21.7	110.9 ± 24.7	0.380
DTm in ms	130.6 ± 23.3	137.3 ± 22.9	0.485
Corrected DTm† in ms	169.4 ± 20.7	162.7 ± 26.3	0.519
S'm in cm/s	8.4 ± 1.9	8.8 ± 1.6	0.551
E'm in cm/s	14.4 ± 2.5	18.9 ± 2.8	0.001
A'm in cm/s	8.6 ± 2.2	6.7 ± 0.9	0.002
E'm/A'm ratio	1.8 ± 0.6	2.9 ± 0.4	0.002
Em/E'm ratio	6.1 ± 2.2	5.6 ± 1.3	0.484
Septum			
Median S's in cm/s (IQR)	7.0 (7.0–8.5)	8.0 (7.25–8.0)	0.204
E's in cm/s	10.6 ± 1.7	14.9 ± 2.2	0.001
Median A's in cm/s (IQR)	6.5 (6.0–7.0)	6.0 (5.25–8.0)	0.037
E's/A's ratio	1.6 ± 0.3	2.6 ± 0.54	0.001
Tricuspid valve			
Median S't in cm/s (IQR)	12.0 (7.5–14.7)	12.0 (12.0–13.0)	0.611
E't in cm/s	14.5 ± 2.7	15.8 ± 1.8	0.141
A't in cm/s	10.6 ± 2.9	10.1 ± 1.8	0.543
E't/A't ratio	1.4 ± 0.38	1.6 ± 0.45	0.217
Pulmonary vein			
Spv in cm/s	52.9 ± 4.6	49.3 ± 8.9	0.288
Dpv in cm/s	51.6 ± 14.0	60.9 ± 11.9	0.080
Apv in cm/s	17.4 ± 3.4	21.1 ± 5.2	0.030
Apvd in ms	68.3 ± 18.4	88.7 ± 17.0	0.018
Spv/Dpv ratio	1.1 ± 0.3	0.8 ± 0.2	0.002
Amd/Apvd ratio	1.6 ± 0.5	1.3 ± 0.4	0.136

SD = standard deviation; OI = osteogenesis imperfecta; Em = peak early mitral valve flow velocity; Am = peak late mitral valve flow velocity; Amd = Am duration; DTm = deceleration time of the Em wave; S'm = peak systolic velocity of the mitral valve; E'm = peak early diastolic velocity of the mitral valve; A'm = peak late diastolic velocity of the mitral valve; S's = peak systolic velocity of the septum; IQR = interquartile range; E's = peak early diastolic velocity of the septum; A's = peak late diastolic velocity of the septum; S't = peak systolic velocity of the tricuspid valve; E't = peak early diastolic velocity of the tricuspid valve; A't = peak late diastolic velocity of the tricuspid valve; Spv = peak systolic velocity of the pulmonary vein; Dpv = peak diastolic velocity of the pulmonary vein; Apv = peak a-wave reversal in the pulmonary vein; Apvd = peak a-wave reversal duration in the pulmonary vein. †Corrected for heart rate.

IVSd, LVPWd, AoAn, AscAo and SinVals diameters (*P* = 0.01, 0.01, 0.04, 0.03, 0.01, 0.01 and 0.03, respectively). In comparison, OI was a significant predictor for IVSd, LVPWd, AoAn, SinVals and Sintubj (*P* = 0.03, 0.01, 0.04, 0.029 and 0.01, respectively). Systolic blood pressure was not a significant predictor for any of the tested independent variables [Table 4].

Discussion

In comparison to control subjects, there was significantly decreased peak early diastolic velocity and its ratio with the peak late diastolic velocity of the lateral mitral valve and upper septum among the studied group of OI patients. In addition, peak late diastolic velocity was significantly increased at the same sites among OI patients. Furthermore, the OI group had lower Em and lower peak a-wave reversal velocity and duration at the pulmonary vein. These findings indicate mild early changes in myocardial diastolic function; however, these changes are not considered as severe as those indicated by the Em/E'm and Amd/Apvd ratios, which were similar in the two groups.

Migliaccio *et al*. compared adult OI patients with controls (n = 40 each) and observed a decrease in the Em velocity and Em/Am ratio with a significant increase in the IVRT and DTm.[13] In the current study, pulmonary vein wave velocity data in OI patients compared to the control subjects showed a significant decrease in the a-wave reversal velocity and duration and an increase in the peak systolic and diastolic ratio. The likely explanation of such changes in OI patients is the greater stiffness of the myocardial tissue and decreased elasticity, leading to echocardiographic changes and altered myocardial relaxation.[11]

While OI is primarily a bone disease, it presents with important extraskeletal abnormalities. Involvement of the heart is due to an alteration in type 1 collagen fibres.[14] Myocardial collagen is primarily made up of collagen type 1, which contributes significantly to the myocardial and aortic wall strength and stiffness.[15] Mutations in OI can directly alter the properties of collagen, either by decreasing synthesis or by altering functional and structural properties.[16–18] Such alterations in the collagen fibres could lead to the abnormalities seen in the myocardial and aortic wall echocardiographic parameters; this has been demonstrated in histological analyses of animal models.[19–21] Radunovic *et al*. reported increased LVIDd, indexed aortic diameters for BSA and mitral and aortic regurgitation in OI adult patients compared to controls.[22] The current study showed that left ventricular dimensions and wall thicknesses were similar between the two groups. However, the OI group had higher dimensions when corrected for BSA.

Table 4: Simple regression analysis of left ventricular and four aortic dimensions of children with *osteogenesis imperfecta* in comparison to an age- and gender-matched control group (N = 32)

Dimension	B regression coefficient (95% CI)						R^2
	OI*	Age	Gender	SBP	DBP	BSA	
LVIDd	-0.51 (-2.92, 3.94)	0.69 (0.07, 1.31)†	-2.70 (-5.06, -0.34)†	0.09 (-0.10, 0.27)	0.19 (-0.05, 0.43)	11.34 (3.05, 19.62)†	0.83
LVISd	0.61 (-3.91, 2.69)	0.09 (-0.51, 0.68)	0.11 (-2.16, 2.38)	0.03 (-0.16, 0.21)	0.09 (-0.14, 0.32)	13.47 (5.50, 21.44)†	0.71
IVSd	-1.49 (-2.80, -0.18)†	-0.19 (-0.43, 0.05)	1.03 (0.13, 1.94)†	0.04 (-0.03, 0.11)	-0.05 (-0.14, 0.05)	3.31 (0.13, 6.48)†	0.33
LVPWd	-1.26 (-2.11, -0.41)†	0.03 (-0.12, 0.19)	-0.44 (-1.03, 0.14)	0.01 (-0.04, 0.05)	-0.07 (-0.13, -0.01)†	2.35 (0.25, 4.37)†	0.57
AoAn	-1.20 (-2.32, -0.08)†	0.20 (-0.01, 0.40)	-0.08 (-0.85, 0.70)	0.02 (-0.04, 0.09)	0.04 (-0.04, 0.12)	5.56 (2.84, 8.28)†	0.86
SinVals	-1.68 (-4.36, 1.00)†	0.15 (-0.34, 0.63)	0.71 (-1.13, 2.56)	-0.01 (-0.16, 0.14)	0.03 (-0.16, 0.22)	7.12 (0.63, 13.59)†	0.72
Sintubj	-2.00 (-3.55, -0.45)†	0.10 (-0.18, 0.38)	1.50 (0.46, 2.59)†	0.09 (-0.01, 0.18)	-0.01 (-0.11, 0.11)	6.14 (2.4, 9.88)	0.77
AscAo	-2.04 (-4.15, -0.08)	0.11 (-0.28, 0.49)	1.14 (-0.31, 2.59)	0.07 (-0.05, 0.18)	0.03 (-0.12, 0.18)	7.14 (2.04, 12.25)†	0.67

CI = confidence interval; OI = osteogenesis imperfecta; SBP = systolic blood pressure; DBP = diastolic blood pressure; BSA = body surface area; LVIDd = left ventricular end diastolic dimensions; LVISd = left ventricular end systolic dimensions; IVSd = interventricular septal thickness at diastole; LVPWd = left ventricular posterior wall thickness in diastole; AoAn = aortic annulus; SinVals = sinus of Valsalva; Sintubj = sinotubular junction; AscAo = ascending aorta.

**In comparison to the control group. †P <0.05.*

This has been similarly reported in both adult and paediatric OI patients.[7,13]

The incidence of mitral valve prolapse in OI is about 3–8%;[6,7] however, none of the patients in the current study had mitral valve prolapse or aortic valve regurgitation. The studied subjects had normal systolic cardiac function and IVRT. There was no significant difference between the OI and control groups regarding the four aortic and pulmonary artery diameters. However, these diameters were significantly larger in the OI group compared to the control subjects when indexed for BSA. Moreover, regression analysis revealed that the diagnosis of OI was a significant predictor for larger left ventricular wall diameters in diastole and a larger diameter of the AoAn, SinVals and Sintubj. Karamifar *et al*. described aortic valve regurgitation in two out of 24 OI patients (8.3%).[23] Radunovic *et al*. reported increased right ventricular outflow tract measurements and main pulmonary artery diameters in adult OI patients when indexed for BSA, indicating involvement of both the right and left sides of the heart.[22] When the significant increase in the four pulmonary artery diameters were indexed to BSA and their Z scores were calculated, the findings of the current study were in line with the findings of Radunovic *et al*.[22] The patients in the current study did not have any systemic illnesses, including hypertension or anaemia to confound the above changes. Moreover, none of the subjects had evidence of pulmonary hypertension.

This study highlights the need for detailed assessments of cardiac function in OI patients who are limited in their physical activities. Early therapeutic modalities could help to treat or modify the progression of the disease to prevent the deterioration of cardiac function. In order to draw a definitive conclusion, large-scale, multicentre research is recommended to assess cardiovascular involvement in children with OI. As there are insufficient data available describing cardiovascular involvement in children with OI, patients in the current study will be followed-up and OI patients with altered diastolic parameters or great vessel dilation will be monitored. Patients with progressive aortic dilation may be prescribed beta blockers and angiotensin receptor blockers as both of these approaches have been suggested to prevent the progression of aortic root dilation in Marfan syndrome.[24]

This study was limited by its small sample size. Additionally, the patients were not symptomatic from a cardiac point of view and no normal values exist for the echocardiographic parameters in this particular group of patients. For this reason, age-matched controls were used for comparative purposes. It was not possible to perform further cardiac function assessments using two-dimensional speckle tracking as only limited echocardiographic views could be obtained due to

chest deformities. Additionally, the echocardiographers performing the scans were not blinded to the study subjects, which may have introduced observer bias. As the majority of the OI subjects were diagnosed with type III OI, it was not possible to analyse the group of OI patients by disease subtype.

Conclusion

The paediatric OI subjects in the current study had normal systolic cardiac function and early changes in myocardial tissue Doppler velocities. This is suggestive of early diastolic cardiac dysfunction. Since these changes may worsen with time, careful cardiological evaluation and follow-up of these patients is warranted. Larger observational TDE studies assessing diastolic function in children with OI are recommended.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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