Original Article

Early myocardial functional abnormalities in primary dyslipidemia: clinical and echocardiographic observations in young children from a highly consanguineous population

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Background: Dyslipidemia is a major health problem among children and adolescents worldwide due to its significant association with cardiovascular disease. Primary dyslipidemias are commonly familial syndromes that can be completely asymptomatic.

Purpose: Apart from the risk of coronary artery disease (CAD), limited data are currently available on the direct effects of dyslipidemia on myocardial function in children.

Methods: We recruited 25 children with primary dyslipidemia (14 with isolated hypercholesterolemia, 4 with isolated hypertriglyceridemia, and 7 with combined dyslipidemia). Relevant clinical manifestations and laboratory and radiological investigations were evaluated. Pulsed-wave Doppler and tissue Doppler imaging echocardiography were performed for all recruited patients and the results were compared with those of 15 age- and sex-matched healthy children.

Results: The median age of the dyslipidemic children was 8 years (range, 1.5–16 years). A family history was documented in 13 cases (52%), while 18 (72%) had consanguineous parents. None of the dyslipidemic children had a personal history or clinical manifestations of CAD. In contrast, echocardiographic findings differed in several diastolic function parameters of both right and left ventricles in dyslipidemic children compared to controls. Based on normalized z scores, aortic valve narrowing was detected in 7 patients (28%), while narrowing of the aortic sinus (sinus of Valsalva) was detected in 15 patients (60%).

Conclusion: Different types of primary dyslipidemia produce functional myocardial abnormalities early in childhood. Biochemical and echocardiographic screening of high-risk children is advised to minimize the incidence of serious cardiovascular complications.

Key words: Primary dyslipidemia, Cardiovascular complications, Pulsed-wave Doppler, Tissue Doppler echocardiography, Child

Key message

In children with primary dyslipidemia, functional myocardial abnormalities can occur at young age, including diastolic functional impairment of both ventricles and narrowing of the aortic valve and the sinus of Valsalva. Echocardiographic evaluations of high-risk children may be as important as biochemical evaluations.

Introduction

Dyslipidaemia is currently a major health problem among children and adolescents, as it predisposes to significant cardiovascular disease. It is defined as the elevation of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides or lipoprotein(a) levels or decreased high-density lipoprotein cholesterol (HDL-C) level.[1] Dyslipidemias are classified into primary and secondary types. Primary dyslipidemias are either due to well-defined genetic causes or due to polygenic hyperlipidemia, in which environmental influences play a role superimposed on a genetic predisposition. Well-defined genetic hyperlipidemias are either autosomal dominant, such as familial hypercholesterolemia with various degrees of penetrance or autosomal recessive, such as in familial hypertriglyceridemia and combined dyslipidemias.[2,3] Clinical manifestations of primary dyslipidemia include xanthomas, xanthelasmata, arcus cornae, and rarely lipemia retinalis, but dyslipidemia could be also asymptomatic. Complications include cardiovascular disease and acute pancreatitis in cases of hypertriglyceridemia. Treatment includes diet therapy, statins for hypercholesterolemia and fibrates for hypertriglyceridemia. Screening in high-risk individuals is very important to detect silent cases and prevent future complications.[4-6]

Data are currently scarce on the direct effects of dyslipidemia on myocardial function in children and adolescents. The current study aims to assess the clinical, laboratory, sonographic,

and particularly echocardiographic features in children and adolescents with primary dyslipidemia before the appearance of coronary artery disease (CAD) manifestations.

Methods

1. Patients

This is a cross-sectional study including 25 patients aged less than 18 years (median, 8 years; range, 1.5–16 years; 14 males) with strong clinico-laboratory evidence of primary dyslipidemiaand 15 age and sex matchedhealthy children (median, 7.5 years; range, 2–16 years; 8 males), who served as control group. The study was conducted in accordance with the declaration of Helsinki for experiments involving humans and approved by the institutional ethics committee at Cairo University Children's Hospital. Written informed consents were obtained from all study participants and/or their legal guardians before recruitment.

2. Clinical evaluation

All recruited patients underwent complete history taking with special emphasis on the age of onset of symptoms if any, age of laboratory diagnosis and the presence of abdominal pain or chest pain. Dyslipidemic children were recruited based on a clearly abnormal lipid profile in the affected child (TC≥200 mg/dL, LDL≥130 mg/dL, triglycerides≥100 mg/dL from 0–9 years and ≥130 mg/dL from 9–18 years and/or HDL≤40 mg/dL), together with suspicious family history (positive consanguinity, family history of similar conditions, previous sudden death, or premature ischemic heart disease in the family), clinical signs of hyperlipidemia, such as xanthomas and xanthelasmas and the absence of secondary causes of dyslipidemia, such as diabetes mellitus, nephrotic syndrome, chronic renal failure, systemic lupus, Kawasaki disease or human immunodeficiency virus infection.[7] Healthy controls were selected based on normal laboratory data and absence of any suspicious family history.

Thorough clinical examination was performed stressing on blood pressure measurement, skin examination (xanthomas, xanthelasma), abdominal examination (hepatomegaly, abdominal tenderness) and cardiac examination to detect any audible murmur. Anthropometric measurements including weight, height, body mass index (BMI), and triceps skin fold thickness were performed. All quantitative measures were plotted on percentile curves for age and sex.[8]

3. Ophthalmological examination

Slit lamp and fundus examination were performed by a specialized pediatric ophthalmologist to detect the presence of lipemia retinalis and/or corneal arcus.

4. Nutritional assessment

Full nutritional history was obtained to reveal dietary habits. After proper diagnosis patients were referred to the clinical nutrition clinic for counseling and medical therapy. Patients were instructed to start diet (skimmed milk, excess fibers, vegetables and low-fat diet stressing on the use of omega 3 rich oils like flaxseed oil) and pharmacological therapy according to the type of lipid profile abnormality.

5. Laboratory parameters

Serum levels of TC, total triglycerides, LDL-C, and HDL-C were assayed after a 12-hour fasting for all patients and their relatives. The lipid profile was measured using direct enzymatic colorimetric methods on Roche Integra Biochemical analyzer with commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). Other assayed laboratory parameters included complete blood count, random blood glucose, and liver enzymes.

6. Abdominal ultrasonography

All hyperlipidemic children underwent abdominal ultrasonography using a 3.5-MHz probe of the device FF sonic (UF-4000) to detect the presence of hepatic echogenicity indicating the probability of a fatty liver,[9] gall bladder stones, or biliary mud.

7. Echocardiography

Echocardiographic assessment was performed for all cases with primary dyslipidemia and healthy controls in the supine and left lateral positions using GE, Vivid-7 system having tissue velocity imaging capabilities, with 3 or 5 MHz probes according to the age of patient. It was performed by a single experienced operator who was blinded to the assigned group of each child. The electrocardiographic cable was connected to the ultrasonography machine to define and to time cardiac cycle events. The examination consisted of M mode, 2-dimensional, pulsed-wave, and color Doppler blood flow velocity measurements of the heart valves. Left ventricular fractional shortening and ejection fraction (EF) were calculated.

Tissue Doppler imaging was obtained from the 4 chambers apical view, and tissue velocities were calculated. Using pulsed tissue velocity indices, the sample volumes were placed in the lateral sides of the mitral and tricuspid annuli and the base of the interventricular septum. The peak systolic and early and late diastolic velocities (Ś, Ė, and Á, respectively) at these points were measured, and the E/Ėratio was calculated. The isovolumic relaxation time and isovolumic contraction time (IVCT) were both measured for both left ventricular and right ventricular lateral walls.

Calculation of global myocardial performance index (MPI) was performed by pulsed tissue velocity imaging. For tissue Doppler, all interval measurements were performed within one cardiac cycle. The MPI was calculated as $(a'-b')/b'$ where a' is the time interval from the end of Á wave to the onset of Ė wave and b' the time from the onset to the end of the Ś wave.[10] Z scores for the various Doppler parameters were also calculated.[11-15]

411 El-koofy NM, et al. Early myocardial defects in primary dyslipidemia

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8. Statistical analysis

SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) and WinPepi statistical software package (ver. 11.65) were used for data analysis. Quantitative data were summarized as means and standard deviations or medians and percentiles for quantitative values, while categorical data were presented as numbers and ratios. Student t test or Mann-Whitney U test were used for the comparison of quantitative data sets as appropriate. Pearson chi-square test was performed for the comparison of categorical data. Numerical correlations were performed using the Pearson correlation coefficient. P values was considered significant if <0.05.

Results

Twenty-five children with primary dyslipidemia from unrelated families were recruited in this study with median age of 8 years (1.5–16 years). The majority of cases were either accidentally discovered (40%), or detected during screening of siblings of a previous case (32%). The remaining cases (28%) were diagnosed after showing characteristic skin manifestations of hyperlipidemia. Males were a little more predominant (56%). Fifty-two percent of families (13 of 25) had a history of similar condition, while 72% of children were born to consanguineous parents. Dyslipidemic children were mostly lean (92%) in accordance with a primary etiology. Arcus cornea was the most common dyslipidemia related clinical finding detected in 10 children (40%), while xanthomas were detected in 8 (32%) and xanthelasma in 6 (24%). Table 1 summarizes the demographic and clinical characteristics of recruited children.

Among our cohort, 56% (14 cases) had hypercholesterolemia, 16% (4 cases) had hypertriglyceridemia and 28% (7 cases) had combined dyslipidemia. Mean hemoglobin level of studied cases was 10.9±0.78 mg/dL. None of the dyslipidemic children were diabetic. There was no significant difference regarding hemoglobin levels, alanine transaminase, aspartate transaminase, and random blood glucose levels between the different categories of recruited children with primary dyslipidemia. The laboratory profiles of recruited children are summarized in Table 2.

Abdominal ultrasonography was performed for all 25 children with primary dyslipidemia and showed that 9 children (36%) had hepatic echogenicity grade II to III, which may indicate either steatosis or steatohepatitis.[9] Seven children (28%) had

Table 1. Demographic and clinical characteristics of children with primary dyslipidemia versus healthy controls

Characteristic	Patients (N=25)	Controls (N=15)	P value
Sex			0.870
Male	14 (56)	8 (53)	
Female	11(44)	6 (40)	
Age (yr)	7.6±4.6	8.1±4.1	0.757
Residence			0.744
Rural	13 (52)	7 (47)	
Urban	12 (48)	8 (53)	
Consanguinity	18 (72)	6 (40)	0.046
Similar condition in the family	13 (52)	0 (0)	0.001
Symptoms			
Chest pain	5 (20)		
Abdominal pain	12 (48)		
Signs			
Cardiac murmur	0 (0)		
Hepatomegaly	1 (4)		
Arcus cornea	10 (40)		
Lipemia retinalis	0 (0)		
Xanthoma	8 (32)		
Xanthelasma	6 (24)		
Blood pressure (BP)			
Systolic BP percentile	71.9±19.5	65.8±18.3	0.333
Diastolic BP percentile	66.3±19.7	63.2±16.8	0.614
Anthropometric measures			
Weight percentile	56.5±21	46.1±24.1	0.160
Height percentile	39.2±26.4	44.4±31.1	0.577
BMI percentile	49.7±25.8	45.3±21.3	0.582
Triceps skin fold thickness percentile	61.9±14.6		
Overweight above 85th percentile	2 (8)	1 (6.7)	0.834

Values are presented as number (%) or mean±standard deviation.
BMI, body mass index.

Table 2. Laboratory investigations of dyslipidemic patients (N=25)

Laboratory parameter	Familial hypercholesterolemia (N=14)	Familial hypertriglyceridemia (N=4)	Combined hyperlipidemia (N=7)	P value
Total cholesterol (mg/dL)	594.4±181.2	169.2±30.7	383.9±170.7	**<0.001**
LDL-cholesterol (mg/dL)	351.2±203.1	117.6±15.8	271.3±125.8	0.069
HDL-cholesterol (mg/dL)	88±34.4	96.8±13.6	75.1±25.4	0.466
TG	157.2±28.6	696±231.2	1346.1±1102.4	**0.001**
Hemoglobin (g/dL)	10.7±0.86	11.2±0.82	11.1±0.7	0.419
ALT (μ/L)	26.4±6.6	23.5±4.8	39±26.2	0.146
AST (μ/L)	29.9±6.1	35.1±15	37.1±12.3	0.261
RBG (mg/dL)	99.8±10.9	94.8±5.1	100±10	0.657

Values are presented as mean±standard deviation.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ALT, alanine transaminase; AST, aspartate transaminase; RBG, random blood glucose.
P values were calculated based on analysis of variance using the WinPepi statistical software package.
Boldface indicates a statistically significant difference with P<0.05.

biliary mud, while none were suffering from gall bladder stones.

For echocardiographic assessment we calculated the z scores of various parameters and we further recruited 15 age and sex-matched healthy children to compare their various measurements and z scores with those of the dyslipidemic children.

We measured aortic root dimensions during echocardiogra-

phic assessment of children with primary dyslipidemia. They were plotted as z scores normalized for age and sex using the equations provided by Campens et al.[16] Dyslipidemic children in our study showed aortic ring diameter ranging from 1 cm to 1.8 cm, diameter of supravalvular ring ranged from 1.3 cm to 2.3 cm and diameter of aortic sinus (sinus of Valsalva) ranged from 1.1 cm to 2.4 cm. After normalization, 7 children showed a narrowed aortic ring (below -2 z score) (3/14 hypercholesterolemia, 2/4 hypertriglyceridemia and 2/7 combined dyslipidemia), 15 childrenshowednarrowing in the sinus of Valsalva (7/14 hypercholesterolemia, 2/4 hypertriglyceridemia, and 6/7 combined dyslipidemia), while none had narrowing of the supravalvular aortic ring (Table 3). None of the dyslipidemic children with narrowing of the aortic ring or the sinus of valslva

Table 3. Aortic root dimensions of dyslipidemic children

Aortic root dimensions	Diameter (cm)	Diameter (z score)	Children with narrowing, n (%)
Aortic ring	1.6 (1.0–1.8)	0.29 (-3.1 to 4.7)	7 (28)
Supravalvular aortic ring	1.8 (1.3–2.5)	1.4 (-0.05 to 4.3)	0 (0)
Sinus of Valsalva	1.7 (1.1–2.4)	-2.5 (-4.7 to 2.8)	15 (60)

A z score below -2 indicated a narrowed ring.

Table 4. Right and left ventricular tissue Doppler findings of patients versus controls

Variable	Doppler value		z score		P value
	Patients (N=25)	Controls (N=15)	Patients (N=25)	Controls (N=15)	
Left ventricle tissue Doppler					
Ě (cm/sec)	20 (18–22)	16.5 (14.5–18.3)	0.76 (0.24–1.15)	-0.19 (-0.73 to 0.34)	**0.003**
Á (cm/sec)	6 (5.5–7.5)	6 (5–6.6)	-0.22 (-0.5 to 0.53)	-0.37 (-0.79 to -0.01)	0.127
Ś (cm/sec)	9 (7.6–9.5)	7.6 (6.2–8.5)	-0.24 (-0.9 to 0.07)	-0.81 (-1.02 to -0.43)	**0.034**
Ě/Á	2.7 (2.4–4)	2.8 (2.5–3.4)	-	-	0.675
IVRT (msec)	43 (39–46)	47 (37–50)	-	-	0.401
IVCT (msec)	39 (36–41)	53 (44–56)	-	-	**<0.001**
MPI	0.3 (0.25–0.34)	0.26 (0.18–0.33)	-	-	0.263
Right ventricle tissue Doppler					
Ě (cm/sec)	18 (15–20.5)	17 (14.6–19.8)	0.45 (-0.5 to 1.1)	0.17 (-0.66 to 0.87)	0.769
Á (cm/sec)	9 (6–11)	9.5 (7.1–10.5)	-0.38 (-1.41 to 0.41)	-0.23 (-1.06 to 0.12)	0.867
Ś (cm/sec)	12 (9.5–13)	14 (12.8–15.5)	-0.7 (-1.9 to 0.1)	-0.1 (-0.5 to 1.1)	**0.043**
Ě/Á	1.9 (1.76–2.3)	1.83 (1.66–2.28)	-	-	0.876
IVRT (msec)	40 (38–49)	36 (34–47)	-	-	0.052
IVCT (msec)	41 (38–52)	49 (47–63)	-	-	**0.031**
MPI	0.32 (0.28–0.34)	0.32 (0.12–0.37)	-	-	0.933
Septum tissue Doppler					
Ě (cm/sec)	15.5 (13.5–16)	14 (12.8–15.2)	0.58 (-0.38 to 1.35)	0.32 (-0.3 to 0.65)	0.184
Á (cm/sec)	6.5 (5.5–7.5)	6 (5–7.5)	0.17 (-0.31 to 0.87)	0.39 (-0.37 to 1.04)	0.769
Ś (cm/sec)	8 (7.5–9)	8 (7.3–9)	0 (-0.07 to 0.61)	0.13 (-0.19 to 0.85)	0.726
Ě/Á	2.3 (2–2.9)	2.5 (1.8–2.6)	-	-	0.695
M mode					
AO (cm)	2.1 (1.6–2.2)	2.1 (1.7–2.3)	1.33 (0.43–2.04)	0.77 (-0.03 to 2.14)	0.608
LA (cm)	2.1 (1.9–2.6)	2.3 (2.1–2.55)	-0.89 (-1.84 to 1.06)	0,23 (-0.5 to 0.69)	0.299
RV (cm)	1 (0.8–1.3)	1.7 (1.2–1.95)	-1.99 (-2.73 to -1.12)	0.73 (-0.12 to 2.15)	**<0.001**
IVS (cm)	0.8 (0.7–0.9)	0.6 (0.5–0.65)	0.42 (-0.51 to 1.14)	-0.44 (-0.82 to 0.84)	0.209
PW (cm)	0.9 (0.7–1.1)	0.5 (0.4–0.6)	1.9 (1.1–3.34)	-0.25 (-1.48 to 0.01)	**<0.001**
LVEDD (cm)	4 (3.2–4.2)	3.7 (3.1–4.1)	-0.72 (-2.53 to 1.56)	-0.04 (-0.74 to 0.42)	0.655
LVESD (cm)	2.4 (2.1–2.6)	2.2 (1.95–2.55)	-0.51 (-2.23 to 1.18)	-0.43 (-0.73 to 0.49)	0.586
FS %	38 (36–43)	43 (36–45)	-	-	0.565
EF %	69 (66–75)	74 (67–77)	-	-	0.356

Values are presented as median (interquartile range).
IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; MPI, myocardial performance index; AO, aortic root dimension; LA, left atrial dimension; RV, right ventricular dimension; IVS, interventricular septal thickness at end-systole; PW, left ventricular posterior wall thickness at end-systole; LVEDD, left ventricular internal dimension at end-diastole; LVESD, left ventricular internal dimension at end-systole; FS, fractional shortening; EF, ejection fraction.
P values were calculated through a 2-tailed Mann-Whitney U test analysis based on the comparison of z scores if calculated and the raw data for ratios if z scores could not be obtained.
Boldface indicates a statistically significant difference with $P<0.05$.

413 El-koofy NM, et al. Early myocardial defects in primary dyslipidemia

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had significant pressure gradient across the left ventricular outflow tract.

Regarding Doppler findings in the M mode, we detected a significant difference concerning the left ventricular posterior wall thickness at end-systole ($P<0.001$), which indicates left ventricular hypertrophy. On the other hand, the most noticeable observation in the tissue Doppler of both ventricles was the significant shortening of the IVCT in both left and right ventricles ($P<0.001$ and $P=0.031$, respectively) (Table 4).

We further correlated major clinical manifestations with positive echocardiographic findings. The presence of xanthoma correlated significantly with IVCT in right ventricular tissue Doppler ($R=0.531$, $P=0.006$). Furthermore, the presence of xanthelasma correlated significantly with the E wave in left ventricular tissue Doppler ($R=0.486$, $P=0.014$), IVCT in right ventricular tissue Doppler ($R=0.585$, $P=0.002$), and IVS in M mode ($R=0.488$, $P=0.013$). Finally, the presence of arcus cornea correlated significantly with E wave in left ventricular tissue Doppler ($R=0.455$, $P=0.022$) and IVCT in right ventricular tissue Doppler ($R=0.647$, $P<0.001$). We also correlated aortic root dimension measurements with various clinical finding; however, there were no detected significant correlations with the presence of xanthomas, xanthelasma or arcus cornea or with the lipid profile parameters.

Discussion

Seventy-two percent of our patients were born to consanguineous parents. Consanguinity is a major problem in Egypt, where it's estimated that 40% of marriages are consanguineous.[17] This clearly indicates that familial dyslipidemias, especially the autosomal recessive, are more prevalent in Egypt. Positive family history of primary dyslipidaemia, early sudden death, and/or premature coronary heart disease was observed in 52% of families.

Forty percent of our patients were completely asymptomatic at recruitment. This observation emphasizes the importance of predictive screening of family members of hereditary dyslipidemia patients even if they are asymptomatic and also to screen relatives of patients who died from myocardial infarction at young age without reasonable cause. Schellack et al.[18] stated that dyslipidemia poses a significant challenge in the pediatric population, mostly due to the fact that serum lipid abnormalities in children are often missed. It has been proposed that the lack of routine screening in children with inherited or acquired dyslipidemias may account for as many as half of them being missed during childhood.

Hyperlipidemia is a major risk factor for CAD and only limited data are available regarding its direct effects on myocardial function apart from CAD. We assessed left ventricular function by pulsed-wave Doppler and tissue Doppler echocardiography in recruited patients and compared the findings with established z scores for many of evaluated parameters and a matched healthy control group. Evidence of left ventricular diastolic dysfunction was detected as tissue Doppler showed that E/É ratio and IVCT were significantly lower in patients than controls. Di Salvo et al.[19] suggested that reductions in longitudinal and circumferential deformation are compensated for by increasing radial strain in children with familial hypercholesterlemia with normal left ventricular EFs in a study conducted on 45 children with hypercholesterolemia.

Assessment of right ventricular function by tissue Doppler of dyslipidemic children showed evidence of impairment of both systolic and diastolic functions. In tissue Doppler, Ś and IVCT were lower in patients than controls. Similarly, studies conducted on adult patients with metabolic syndrome detected right ventricular remodeling.[20]

The systolic function as assessed by EF in M mode in our patients was normal. The only morphological changes detected by M mode were septal and left ventricular hypertrophy with significant difference between patients and controls, which came in agreement with the results of the study conducted on children aged 7–18 years with hypercholesterolemia and demonstrated that left ventricular hypertrophy can be also seen at younger ages.[21]

In our study, we detected aortic valve narrowing in almost 30% of studied patients from all 3 categories of dyslipidemia. Several studies demonstrated previously that hypercholesterolemia is related to increased risk of aortic valve calcification and that preventive treatment of hypercholesterolemia could play an important role to decrease or inhibit development of aortic valve calcification,[22-24] thus, it is expected that early preventive measures during childhood could minimize aortic valve involvement.

In contrast to adult studies of dyslipidemia, we did not detect supravalvular aortic stenosis in our dyslipidemic children.[25] This, may be attributed to the young age of our patients. On the other hand, we detected narrowing of the sinus of Valsalva in the majority of our dyslipidemic patients (60%), which came in agreement with previous results obtained also in familial hypercholesterolemia.[26] We further detected that the majority of cases with combined dyslipidemia in our cohort showed narrowing of the sinus of Valsalva (86%) compared to only 50% in children with isolated hypercholesterolemia and 50% of children with isolated hypertriglyceridemia.

The study has some limitations, mainly the low number of recruited children with primary dyslipidemias; however, being rare disorders, it was extremely difficult to recruit a higher number of patients within a reasonable time frame. Another limitation is the cross-sectional nature of the study, which limits the follow-up of the progression of the subtle echocardiographic functional defects detected in children into symptomatic cardiovascular disease later in life. Finally, the inconclusiveness in some of the parameters measured may require more advanced echocardiographic technologies, such as the 4-dimensional speckle tracking to get more evidence on the early development of the diastolic dysfunction in dyslipidemic children.

In conclusion, data available about myocardial defects of primary dyslipidemia are mostly obtained from studies in adults and inpatients with familial hypercholesterolemia, thus, there are limited data about the effects of different types of dyslipidaemias particularly in children. Here, we show that these complications exist in all types of primary dyslipidemias, particularly impaired diastolic functions of both ventricles, and narrowing of aortic valve and sinus of Valsalva. Thus, early echocardiographic screening of dyslipidemic children and their family members should be as essential as biochemical screening.

See the commentary on "Early echocardiographic screening for subclinical myocardial dysfunction in children and adolescents with dyslipidemia: why and when?" via https://doi.org/10.3345/cep.2022.00031.

Footnotes

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