Evaluation of arterial stiffness and carotid intima-media thickness in children with primary and renal hypertension

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Abstract

Hypertension is an increasing disease in children and the risk of endothelial damage and target organ damage increases in the presence of additional risk factors such as obesity. In our study, early atherosclerotic changes and target organ damage were investigated in hypertensive children. Twenty four-hour ambulatory pulse wave analysis was performed by oscillometric method in 17 patients with primary hypertension, 18 obese patients with primary hypertension, and 16 patients with renal hypertension. Carotid intima- media thickness and left ventricular mass index were measured. The control group included 20 age- and sex-matched healthy children. Central systolic blood pressure, central diastolic blood pressure, systolic blood pressure and diastolic blood pressure were higher in the primary hypertension group compared to controls ($p = 0.001$, $p = 0.005$, $p = 0.001$, $p = 0.009$, respectively), central systolic blood pressure was higher in the renal hypertension group than the control group ($p = 0.018$). There was no difference between the two groups in terms of pulse wave analysis parameters, carotid intima-media thickness, or left ventricular mass index ($p > 0.05$). Pulse wave velocity was positively correlated with systolic blood pressure, diastolic blood pressure, central systolic blood pressure, central diastolic blood pressure ($p < 0.001$). Augmentation index was positively correlated with DBP and cDBP ($p = 0.01$, $p = 0.002$, respectively). Our findings show that high blood pressure is associated with arterial stiffness and target organ damage. Pulse wave analysis is a reliable and non-invasive method that can be used to prevent target organ damage in hypertensive children by detecting early atherosclerotic changes and thus allowing to take necessary precautions such as lifestyle changes.

Introduction

Hypertension has an increasing prevalence in children and adolescents. Childhood hypertension is an important risk factor for cardiovascular system diseases, chronic renal failure, and cerebrovascular diseases in adulthood [1]. In the etiology of hypertension, secondary causes are more common in the first years of life, although primary hypertension is observed more frequently in the following years [2]. Renal parenchymal diseases are the most common cause of secondary hypertension in children [3].

Hypertension causes target organ damage by changing the structural and functional properties of arteries. Although morbid cardiovascular events are rare in pediatric patients, it is important to identify hypertensive children at risk for complications later in life. Some target organ damage markers are used for this purpose, such as left ventricular hypertrophy and increased carotid intima-media thickness (CIMT) [4]. Research on children with hypertension has reported that CIMT is increased compared to healthy controls and this increase is much more pronounced in the association of hypertension and obesity [5].

Arterial stiffness is an indicator of atherosclerosis and occurs due to thickening and loss of elasticity of the arterial wall. It is a precursor to target organ damage and increased cardiovascular events [6]. The measurement of pulse wave velocity (PWV) was first proposed by the European Society of Hypertension-European Society of Cardiology (ESH-ESC) in 2003 to determine arterial stiffness [7]. A small number of studies have shown that PWV is increased in children with obesity and hypertension [7–9].

Evaluation of subclinical end organ damage caused by hypertension in children will enable to identify future cardiovascular diseases and to reduce the possibility of end organ damage by taking lifestyle precautions in these individuals. Therefore, in our study, it was planned to measure PWV, augmentation index (AIx), central and peripheral blood pressure values by 24-hour ambulatory pulse wave analysis with oscillometric method, CIMT by ultrasonographic method, and left ventricular mass index (LVmass index) by M-mode echocardiography (ECHO) in children with primary and renal hypertension and to investigate whether these variables differ from an age- and sex-matched healthy control group.

Materials And Method

The study included 35 patients who were followed up with the diagnosis of primary hypertension in the Department of Pediatric Cardiology and 16 patients with the diagnosis of renal hypertension in the Department of Pediatric Nephrology, Faculty of Medicine, Eskisehir Osmangazi University. The control group consisted of 20 healthy children who applied to the Department of Pediatric Cardiology with nonspecific chest pain.

The study was conducted prospectively. The families of the children were informed about the purpose and method of the study and their written consent was obtained regarding their voluntary participation. The study protocol was approved by the Faculty of Medicine Ethics Committee at Eskisehir Osmangazi University with the decision numbered 80558721/59 and dated 27.06.2019.

The children were divided into 4 groups as non-obese subjects with primary hypertension (PH group, n: 17), obese subjects with primary hypertension (OPH group, n: 18), subjects with renal hypertension (RH group, n: 16), and healthy subjects (control group, n: 20). The children's medical history, background, and family history were questioned and physical examinations were performed. Children with a history of congenital heart disease, diabetes, or any other chronic disease and those who had a condition that required medication other than antihypertensive treatment were excluded.

Echocardiographic examinations were performed by an experienced pediatric cardiologist in the Department of Pediatric Cardiology using a Philips Epiq 3D ultrasound device. Left ventricular mass (LVmass) was calculated by Penn-Cube formula (LVmass = 1.04 [(LVEDd + IVSD + LVPWd)3- (LVEDd)3]-13.6) [10]. LVmass index was calculated by dividing LVmass by the body surface area. Relative wall thickness (RWTh) was calculated using the formula RWTh = 2xPWd/LVEDd [11].

CIMT measurement was performed in all patients using a Vivid I color Doppler ultrasonography device with a 12 MHz linear probe. The subjects were placed on supine position and a thin pillow was placed under their necks and then, their necks were turned to the opposite side. A 1 cm segment was determined within the first 2 cm distal region from the common carotid artery bulb and the images were transferred to the computer environment. Based on the far wall measurement method with a special CIMT measurement software, the mean, maximum, and minimum values of the segments were determined [12]. These measurements were repeated for both main carotid arteries and mean values were obtained.

The patients were weighed on a calibrated electronic scale (SECA digital scale, sensitive to 0.1 kg) with thin clothes and no shoes. Height measurements were made with a Harpenden stadiometer (sensitivity to 0.1 cm) in standing upright position, with bare feet and feet adjacent and parallel, and shoulders and the gluteal region in contact with the wall. Body mass index (BMI) was calculated using height and weight measurements [weight (kg)/height² (m²)]. According to the percentile curves determined by the World Health Organization, those with a body mass index in the 95th percentile and above were considered obese [13].

Serum glucose, insulin, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), total cholesterol, triglyceride, uric acid, and C-reactive protein (CRP) levels were measured after 12 hours of fasting. Spot urine microalbumin/creatinine ratio was measured. Glomerular filtration rate (GFR) was calculated using the Schwartz formula (Schwartz formula: κ x height/serum creatinine). κ was determined as 0.55 in children and adolescent girls and 0.7 in adolescent boys [14]. Homa-IR was calculated as fasting glucose (mg/dL) x fasting insulin (uIU/mL)/405 [15].

Mobil-O-Graph (IEM, Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft mbH, Stolberg, Germany) pulse wave analysis monitor was used for 24-hour automatic pulse wave analysis monitoring by the oscillometric method. The children were recommended not to do heavy exercise before monitoring and not to take any caffeinated beverages or medical treatment the day before. A cuff of the appropriate size for the children's age and upper arm circumference was tied. The device was set at a protocol to measure every 20 minutes during daytime (when the children are awake) and once every 30 minutes during night time (when the children are asleep). The Hypertension Management Software Client Server (HMS-CS) version 2.0 was used for the transfer and analysis of the measurements.

Data analysis was done with IBM SPSS 21 software. Data with normal distribution are shown as mean ± standard deviation and data with non-normal distribution are shown as median (Q1-Q3). The conformity of quantitative variables to normal distribution was evaluated with the Shapiro Wilk test. Four groups with normal distribution were compared with one-way analysis of variance. For values that differed significantly according to one-way analysis of variance, pairwise comparisons were performed with the Tukey test. Comparisons of four groups with non-normal distribution were evaluated with the Kruskal Wallis H test. For values that differed significantly according to the Kruskal Wallis H test, pairwise comparisons were done with Dunn's test. Pearson chi-squared analysis was used to analyze the cross tables. Spearman correlation analysis was used for variables with non-normal distribution to determine the strength and direction of the correlations between the variables. $P < 0.05$ was considered significant in all analyses.

Results

Our study was carried out with a total of 71 children aged 8–18 years, 17 of whom had primary hypertension, 18 had both primary hypertension and obesity, and 16 had renal hypertension. Twenty healthy normotensive children were included as the control group. The demographic characteristics of the groups are given in Table 1. The OPH group had a statistically higher median weight than the control and PH groups ($p = 0.016$, $p = 0.002$, respectively) and higher mean BMI than the control, PH, and RH groups ($p < 0.001$ for all). There was no statistically significant difference between the groups in terms of age, sex, height, fasting blood glucose, insulin, HOMA-IR, total cholesterol, triglyceride, HDL-C, LDL-C, CRP, uric acid, microalbumin/creatinine ratio in spot urine, or GFR. ($p > 0.05$).

Table 1
Demographic and biochemical data

		PH (n = 17)	OPH (n = 18)	RH (n = 16)	Control (n = 20)	p
Sex	**Female**	8 (%47.1)	5 (%27.8)	4 (%25)	11 (%55)	0.42
	Male	9 (%52.9)	13 (%72.2)	12 (%75)	9 (%45)	
Age (year)		13.9 (11.8–15.9)	14 (10.6–14.4)	15 (12–16)	14.6 (13.3–16)	0.42
Height (cm)		162 (157–165)	165 (152–174)	161 (157–174)	165 (160–169)	0.84
Weight (kg)		53 (46–55)[a]	81.5 (64–97)[a,b]	62 (50.5–68.5)	58.2 (43.5–65.5)[b]	**0.002**
BMI (kg/m²)		20.4 ± 2.6[c]	29.2 ± 4[c,d,e]	22.5 ± 3.1[d]	20.8 ± 5.1[e]	**0.001**
Fasting blood glucose (mg/dL)		88 (82–90)	82.5 (81–86)	82.5(78–88)	84.5 (79.5–87.5)	0.43
Insulin (uIU/mL)		15.2 (13.2–19.3)	19.2 (9–37)	10.4 (7.6–18.7)	12.8 (7.8–20.3)	0.21
Homa-IR (uIU/mL**)**		3.1 (2.5–4.6)	3.74 (2.46–6.71)	2.26 (1.5-4)	2.55 (1.63–3.96)	0.25
Total cholesterol (mg/dL)		153 (140–172)	148 (130–162)	145 (127–158)	143.5 (123–157)	0.35
Triglyceride (mg/dL)		101 (74–130)	109 (83–118)	90 (66.5–128)	84.5 (62–136)	0.79
HDL-C (mg/dL)		51 (42–60)	44 (41–49)	42.5 (41–47)	49 (41–55)	0.15
LDL-C (mg/dL)		96.1 (88.4–114)	95 (83–110)	89.6 (80.1–98.6)	77 (66.7–105)	0.17
CRP (mg/L)		0.4 (0.3–0.9)	1.75 (0.4-3)	1.15 (0.3–5.5)	0.4 (0.3–1.6)	0.2
Uric acid (mg/dL)		4.7 ± 1	4.9 ± 2	5.2 ± 1.56	4.6 ± 1.2	0.65
Microalbumin/creatinine (mg/g)		7.5 (3.6–15)	6.5 (2.4–9.4)	7.6 (4.5–25.8)	6.8 (4-16.8)	0.67
GFR (mL/min)		166 (143–175)	160 (139–181)	135 (113–165)	162 (148–185)	0.58

Normally distributed parameters are given as mean ± SD and non-normally distributed parameters are given as median (25%-75%). PH: primary hypertension, OPH: obesity and primary hypertension, RH: renal hypertension, BMI: body mass index, homa-IR: homeostatic model assessment–insulin resistance, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, CRP: C-reactive protein, GFR: glomerular filtration rate. For values that differed significantly according to analysis of variance, pairwise comparisons were performed with the Tukey test. For values that differed significantly according to the Kruskal Wallis H test, pairwise comparisons were done with Dunn's test.

a PH group and OPH group p = 0.002

b OPH group and control group p = 0.016

c PH group and OPH group p < 0.001

d OPH group and RH group p < 0.001

e OPH group and control group p < 0.001

Mean duration after the diagnosis of hypertension was 22.2 ± 21.8 months in the PH group, 17.5 ± 22.8 months in the OPH group, and 26.3 ± 27 months in the RH group, with no statistically significant difference (p > 0.05). Evaluating all study groups together, no significant correlation was found between the duration of hypertension and pulse wave analysis parameters or CIMT values (p > 0.05).

In the PH group, 8 patients (47%) were using angiotensin converting enzyme (ACE) inhibitors, 5 (29.4%) calcium channel blockers (CCB), and 4 (23.5%) no medication. In the OPH group, 4 patients (22.2%) were using ACE inhibitors, 4 (22.2%) CCB, and 10 (55.5%) no medication. In the RH group, 7 patients (43.7%) were using CCB, 2 (12.5%) ACE inhibitors, 4 (25%) dual antihypertensive therapy (CCB and ACE inhibitors), and 3 (18.7%) no medication.

In the RH group, 8 patients had unilateral kidney atrophy, 1 had multicystic dysplastic kidney, 1 had Alport syndrome, 1 had nephrolithiasis and hydronephrosis, 4 had reflux nephropathy, and 1 had renal artery stenosis.

Fundus examinations revealed stage 1 retinopathy in 1 patient and stage 2 retinopathy in 2 patients in the OPH group, stage 1 retinopathy in 2 patients in the PH group, and stage 1 retinopathy in 2 patients in the RH group.

Renal function tests, renal ultrasonography, and renal Doppler ultrasonography findings were normal in the PH and OPH groups.

LVmass index, IVSDd, LVEDd, and LVPWd measurements were within normal limits according to body surface area in all study and control subjects. Two patients in the OPH group, 3 in the PH group, and 1 in the RH group had an RWT value above 0.42. Ejection fraction and shortening fraction values were above

normal in 2 patients in the RH group and shortening fraction was above normal in 1 patient in the PH group. No cardiomyopathy was observed in any subject of the all groups.

Pulse wave analysis parameters were statistically compared between the study and control groups (Table 2). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were statistically higher in the PH group than the control group (p = 0.001, p = 0.009, p = 0.002, respectively). MAP was statistically higher in the RH group compared to controls (p = 0.038). Central systolic blood pressure (cSBP) was found to be statistically higher in the PH and RH groups compared to the control group (p = 0.001, p = 0.018, respectively). Central diastolic blood pressure (cDBP) was statistically higher in the the PH group than the control group (p = 0.005). AIx was higher in the PH group than all the other groups, albeit not with statistical significance (p = 0.07). There was no statistically significant difference between the groups in terms of heart rate (HR), pulse pressure (PP), reflection magnitude (RM), peripheral resistance (PR), or PWV (p > 0.05).

Table 2
Comparison of pulse wave analysis parameters

	PH (n = 17)	OPH (n = 18)	RH (n = 16)	CONTROL (n = 20)	P
SBP (mmHg)	123.2 ± 10.5[a]	118.7 ± 7.8	119.8 ± 8.2	112.6 ± 6.4[a]	**0.002**
DBP (mmHg)	73 (65–75)[b]	66.5 (64–71)	68 (65–71)	64 (61.5–68.5)[b]	**0.01**
MAP (mmHg)	94.8 ± 6.9[c]	90.3 ± 6.9	92.7 ± 6.6[d]	86.9 ± 4.7[c,d]	**0.002**
HR (beat/min)	85.8 ± 13	81.2 ± 7.1	77.7 ± 8	80.5 ± 8.3	0.1
PP (mmHg)	51 (45–61)	51 (50–53)	49.5 (43-56.5)	46.5 (42–51)	0.06
cSBP (mmHg)	107.3 ± 7.2[e]	104 ± 6.6	105.4 ± 7.1[f]	98.8 ± 4.8[e,f]	**0.001**
cDBP (mmHg)	76 (67–78)[g]	69 (66–75)	70.5 (66.5–72)	65.5 (63.5–70)[g]	**0.01**
AIx (%)	23.2 ± 8.5	18.3 ± 5.9	17.3 ± 6.1	19.1 ± 6.3	0.07
PR (s.mmHg/mL)	1.1 (1.1–1.2)	1.1 (1-1.1)	1.1 (1-1.2)	1.1 (1-1.1)	0.2
RM (%)	56.6 ± 6.7	57.7 ± 6.4	57.4 ± 6.2	56.3 ± 5.7	0.8
PWV (m/sec)	4.9 (4.7–5.1)	4.8 (4.6-5)	4.8 (4.6-5)	4.6 (4.4–4.9)	0.4
Normally distributed parameters are given as mean ± SD and non-normally distributed parameters are given as median (25%-75%). PH: primary hypertension, OPH: obese and primary hypertension, RH: renal hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, PP: pulse pressure, cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, AIx: augmentation index, PR: peripheral resistance, RM: reflection magnitude, PWV: pulse wave velocity. For values that differed significantly according to analysis of variance, pairwise comparisons were performed with the Tukey test. For values that differed significantly according to the Kruskal Wallis H test, pairwise comparisons were done with Dunn's test.					
a PH group and control group p = 0.001					
b PH group and control group p = 0.009					
c PH group and control group p = 0.002					
d RH group and control group p = 0.038					
e PH group and control group p = 0.001					
f RH group and control group p = 0.018					
g PH group and control group p = 0.005					

CIMT and ECHO parameters were statistically compared between the study and control groups (Table 3). IVSDd was statistically higher in the OPH and RH groups than the control group (p = 0.02, p = 0.014, respectively). Mean LVmass was statistically higher in the OPH group compared to the controls (p = 0.016). There was no statistically significant difference between the groups in terms of the other echocardiographic parameters or CIMT values (p > 0.05).

Table 3
Comparison of ECHO parameters and CIMT measurements

	PH (n = 17)	OPH (n = 18)	RH (n = 16)	CONTROL (n = 20)	P
IVSDd (mm)	8.26 ± 0.95	8.57 ± 1.67[a]	8.71 ± 1.22[b]	7.39 ± 1.11[a,b]	**0.01**
LVEDd (mm)	43.35 ± 3.94	45.47 ± 3.56	44.38 ± 3.88	42.91 ± 4.73	0.23
LVPWd (mm)	7.79 ± 1.57	8.0 ± 1.60	7.93 ± 0.76	7.18 ± 1.25	0.2
LV mass (g)	108.65 ± 25.78	124.89 ± 37.35[c]	117.56 ± 21.17	95.80 ± 28.64[c]	**0.02**
LVmass index (g/m²)	70.21 ± 14.23	66.44 ± 15.27	71.75 ± 9.91	60.60 ± 11.78	0.54
RWT	0.34 (0.29–0.4)	0.34 (0.31–0.37)	0.36 (0.33–0.37)	0.32 (0.30–0.38)	0.68
CIMT right (mm)	0.41 (0.4–0.44)	0.44 (0.41–0.45)	0.41 (0.4–0.44)	0.41 (0.4–0.43)	0.35
CIMT left (mm)	0.42 (0.4–0.44)	0.44 (0.41–0.46)	0.42 (0.4–0.46)	0.42 (0.4–0.44)	0.68

Normally distributed parameters are given as mean ± SD, and non-normally distributed parameters are given as median (25%-75%). IVSDd: interventricular septum end-diastolic thickness, LVEDd: left ventricular end-diastolic diameter, LVPWd: left ventricular end-diastolic posterior wall thickness, LVmass: left ventricular mass, RWT: relative wall thickness, CIMT: carotid intima-media thickness. For values that differed significantly according to analysis of variance, pairwise comparisons were performed with the Tukey test. For values that differed significantly according to the Kruskal Wallis H test, pairwise comparisons were done with Dunn's test.

a OPH group and control group p = 0.02

b RH group and control group p = 0.014

c OPH group and control group p = 0.016

Regarding the correlations between pulse wave analysis parameters and anthropometric measurements across all groups (n = 71) (Table 4), SBP was positively correlated with age, height, weight, and BMI (p = 0.05, p = 0.01, p < 0.001, p = 0.004, respectively). MAP was positively correlated with age, height, and weight (p = 0.04, p = 0.05, p = 0.02, respectively). PP was found to be positively correlated with height, weight, and BMI (p = 0.02, p < 0.001, p < 0.001, respectively). cSBP was positively correlated with age, height, weight, and BMI (p = 0.02, p = 0.04, p = 0.002, p = 0.008, respectively). AIx was negatively correlated with age, height, and weight (p = 0.02, p < 0.001, p = 0.04, respectively). PR was negatively correlated with height (p = 0.01), as was RM (p = 0.01). Finally, PWV was found to be positively correlated with height, weight, and BMI (p = 0.003, p = 0.001, p = 0.003, respectively).

Table 4
Correlations between pulse wave analysis parameters and anthropometric measurements

	Age		Height		Weight		BMI	
	r	p	r	p	r	p	r	p
SBP (mmHg)	0.23	**0.05**	0.29	**0.01**	0.40	**< 0.001**	0.33	**0.004**
DBP (mmHg)	0.21	0.07	0.14	0.23	0.09	0.46	0.01	0.93
MAP (mmHg)	0.24	**0.04**	0.23	**0.05**	0.27	**0.02**	0.21	0.08
HR (beat/min)	-0.20	0.09	-0.20	0.08	-0.04	0.76	0.10	0.40
PP (mmHg)	0.09	0.43	0.25	**0.03**	0.49	**< 0.001**	0.49	**< 0.001**
cSBP (mmHg)	0.26	**0.02**	0.23	**0.04**	0.36	**0.002**	0.31	**0.008**
cDBP (mmHg)	0.17	0.13	0.08	0.46	0.09	0.45	0.04	0.74
AIx(%)	-0.26	**0.02**	-0.45	**< 0.001**	-0.24	**0.04**	-0.06	0.61
PR (s.mmHg/mL)	-0.08	0.52	-0.29	**0.01**	-0.21	0.07	-0.17	0.15
RM (%)	-0.11	0.33	-0.29	**0.01**	-0.15	0.21	-0.03	0.83
PWV (m/sec)	0.22	0.06	0.34	**0.003**	0.40	**0.001**	0.34	**0.003**

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, PP: pulse pressure, cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, AIx: augmentation index, PR: peripheral resistance, RM: reflection magnitude, PWV: pulse wave velocity. BMI: body mass index.

Regarding the correlations between SBP, DBP, MAP, HR, PP, cSBP, cDBP values and AIx, PR, RM, and PWV (Table 5), SBP was positively correlated with both PR and PWV ($p = 0.04$, $p < 0.001$, respectively). DBP was positively correlated with AIx, PR, and PWV ($p = 0.01$, $p < 0.001$, $p < 0.001$, respectively). MAP was found to be positively correlated with AIx, PR, and PWV ($p = 0.02$, $p < 0.001$, $p < 0.001$, respectively). HR was positively correlated with AIx ($p < 0.001$) and negatively correlated with RM ($p = 0.03$). PP was negatively correlated with both PR and RM ($p = 0.01$, $p = 0.01$, respectively) and positively correlated with PWV ($p < 0.001$). cSBP was found to be positively correlated with both PR and PWV ($p = 0.002$, $p < 0.001$, respectively). Finally, a positive correlation was found between mDBP and AIx, PR, and PWV ($p = 0.002$, $p < 0.001$, $p < 0.001$, respectively).

Table 5
Correlations of SBP, DBP, MAP, HR, PP, cSBP, and cDBP with AIx, PR, RM, and PWV

	AIx		PR		RM		PWV	
	r	p	r	p	r	p	r	p
SBP (mmHg)	0.17	0.15	0.24	**0.04**	-0.21	0.07	0.81	**< 0.001**
DBP (mmHg)	0.29	**0.01**	0.58	**< 0.001**	0.01	0.91	0.6	**< 0.001**
MAP (mmHg)	0.25	**0.02**	0.45	**< 0.001**	-0.10	0.37	0.78	**< 0.001**
HR (beat/min)	0.71	**< 0.001**	0.04	0.68	-0.25	**0.03**	0.09	0.41
PP (mmHg)	-0.09	0.45	-0.29	**0.01**	-0.3	**0.01**	0.48	**< 0.001**
cSBP (mmHg)	0.23	0.05	0.35	**0.002**	0.07	0.55	0.75	**< 0.001**
cDBP (mmHg)	0.36	**0.002**	0.5	**< 0.001**	-0.009	0.94	0.58	**< 0.001**

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, PP: pulse pressure, cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, AIx: augmentation index, PR: peripheral resistance, RM: reflection magnitude, PWV: pulse wave velocity.

Concerning the correlations between echocardiographic parameters, CIMT measurements and anthropometric measurements (Table 6), IVSDd, LVEDd, LVPWd, and LVmass were positively correlated with age, height, weight, and BMI. However, age and anthropometric measurements were not correlated with the other echocardiographic parameters or CIMT measurements.

Table 6
Correlations of anthropometric measurements with echocardiographic parameters and CIMT measurements

	Age		Height		Weight		BMI	
	r	p	r	p	r	p	r	p
IVSDd (mm)	0.31	**0.007**	0.38	**0.001**	0.51	**< 0.001**	0.44	**< 0.001**
LVEDd (mm)	0.39	**0.001**	0.53	**<0.001**	0.56	**< 0.001**	0.36	**0.002**
LVPWd (mm)	0.28	**0.01**	0.31	**0.008**	0.42	**< 0.001**	0.36	**0.002**
LVmass (g)	0.46	**< 0.001**	0.53	**< 0.001**	0.64	**< 0.001**	0.49	**< 0.001**
LVmass index (g/m²)	0.10	0.37	0.06	0.62	0.04	0.75	-0.01	0.92
RWT (mm)	0.12	0.31	0.02	0.84	0.13	0.25	0.19	0.10
CIMT right (mm)	-0.20	0.86	-0.05	0.64	0.07	0.55	0.18	0.13
CIMT left (mm)	-0.03	0.81	-0.11	0.35	0.03	0.78	0.12	0.30

IVSDd: interventricular septum end-diastolic thickness, LVEDd: left ventricular end-diastolic diameter, LVPWd: left ventricular end-diastolic posterior wall thickness, LVmass: left ventricular mass, RWT: relative wall thickness, CIMT: carotid intima-media thickness, BMI: body mass index.

Considering the correlations between pulse wave analysis parameters and biochemical parameters (Table 7), SBP was positively correlated with homa-IR, serum insulin, and uric acid levels ($p < 0.001$, $p < 0.001$, $p = 0.009$, respectively). DBP was negatively correlated with CRP levels ($p = 0.01$). MAP was positively correlated with serum insulin and homa-IR levels ($p = 0.01$, $p = 0.02$, respectively). PP was found to be positively correlated with fasting blood glucose, homa-IR, serum insulin, and uric acid levels ($p = 0.002$, $p < 0.001$, $p < 0.001$, $p = 0.001$, respectively). cSBP was positively correlated with both homa-IR and serum insulin levels ($p < 0.001$, $p < 0.001$, respectively). cDKB was negatively correlated with CRP ($p = 0.02$). AIx was positively correlated with serum total cholesterol levels and negatively correlated with uric acid levels ($p = 0.04$, $p = 0.001$, respectively). PWV was positively correlated with homa-IR, serum insulin, and uric acid

levels (p = 0.007, p = 0.005, p = 0.02, respectively). However, pulse wave analysis parameters were not correlated with serum HDL-C, LDL-C, triglyceride, spot urine microalbumin/creatinine ratio, or GFR (p > 0.05). Again, no correlation was found between CIMT measurements and any of the biochemical parameters, except for a weak positive correlation between CIMT right and fasting blood glucose (r = 0.25, p = 0.03).

Table 7
Correlations between pulse wave analysis parameters and biochemical parameters

	Fasting blood glucose		Insulin		Homa-IR		Total cholesterol		HDL-C		LDL-C		Triglyceride		CRP		Uric
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r
SBP (mmHg)	0.21	0.08	0.41	**< 0.001**	0.42	**< 0.001**	-0.002	0.98	-0.08	0.51	0.03	0.78	0.08	0.51	-0.14	0.21	0.30
DBP (mmHg)	-0.11	0.34	0.07	0.53	0.05	0.65	0.08	0.51	0.12	0.31	0.10	0.38	-0.13	0.27	-0.30	**0.01**	-0.01
MAP (mmHg)	0.04	0.71	0.28	**0.01**	0.27	**0.02**	0.07	0.58	0.03	0.77	0.10	0.39	-0.002	0.98	-0.22	0.06	0.15
HR (beat/min)	0.09	0.47	0.10	0.38	0.10	0.41	0.21	0.72	0.06	0.61	0.19	0.1	0.16	0.16	-0.12	0.28	-0.19
PP (mmHg)	0.35	**0.002**	0.48	**< 0.001**	0.51	**< 0.001**	-0.07	0.53	-0.18	0.11	-0.03	0.81	0.13	0.28	0.11	0.32	0.40
cSBP (mmHg)	0.16	0.17	0.40	**< 0.001**	0.40	**< 0.001**	-0.02	0.85	-0.01	0.91	0.04	0.69	-0.03	0.75	-0.19	0.09	0.22
cDBP (mmHg)	-0.02	0.84	0.14	0.23	0.12	0.29	0.04	0.71	0.10	0.39	0.10	0.39	-0.18	0.11	-0.26	**0.02**	-0.01
AIx(%)	0.03	0.81	0.10	0.38	0.09	0.45	0.25	**0.04**	0.22	0.06	0.19	0.09	0.006	0.96	-0.17	0.14	-0.38
PR (s.mmHg/m)	-0.10	0.36	0.01	0.92	-0.10	0.93	0.22	0.06	0.22	0.06	0.19	0.1	-0.03	0.76	-0.18	0.11	-0.21
RM (%)	-0.14	0.21	0.03	0.79	0.01	0.88	0.01	0.94	0.12	0.28	0.02	0.86	-0.07	0.56	0.05	0.67	-0.21
PWV (m/sec)	0.05	0.69	0.32	**0.005**	0.31	**0.007**	-0.08	0.48	-0.12	0.28	-0.04	0.72	0.01	0.88	-0.18	0.12	0.26

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, PP: pulse pressure, cSBP: central systolic blood press
AIx: augmentation index, PR: peripheral resistance, RM: reflection magnitude, PWV: pulse wave velocity, homa-IR: homeostatic model assessment–insulin res
cholesterol, LDL-C: low-density lipoprotein-cholesterol, CRP: C-reactive protein, GFR: glomerular filtration rate. Correlations between variables with non-normal
correlation analysis.

Concerning the correlations between pulse wave analysis parameters and both ECHO and CIMT measurements (Table 8), SBP was positively correlated with IVSDd, LVPWDd, LVmass, and RWT (p < 0.001, p < 0.001, p = 0.001, p = 0.007 respectively). DBP was positively correlated with IVSDd, LVPWDd, LVmass, and LVmass index (p = 0.01, p = 0.008, p = 0.02, p = 0.002 respectively). MAP was found to be positively correlated with IVSDd, LVPWDd, LVmass, LVmass index, and RWT (p < 0.001, p < 0.001, p = 0.001, p = 0.006, p = 0.009 respectively). PP was positively correlated with IVSDd, LVPWDd, LVmass, and RWT (p = 0.001, p = 0.01, p = 0.005, p = 0.03 respectively). cSBP was positively correlated with IVSDd, LVPWDd, LVmass, LVmass index, and RWT (p < 0.001, p < 0.001, p < 0.001, p = 0.02, p = 0.008 respectively). cDBP was found to be positively correlated with IVSDd, LVPWDd, LVmass, and LVmass index (p = 0.009, p = 0.01, p = 0.02, p = 0.002 respectively). AIx was positively correlated with LVEDd, CIMT (right) and CIMT (left) (p = 0.02, p = 0.02 p = 0.05 respectively) and negatively correlated with LVmass (p = 0.01). RM was positively correlated with CIMT (right) and CIMT (sol) (p = 0.007, p = 0.01 respectively). PWV was found to be positively correlated with IVSDd, LVPWDd, LVmass, and RWT (p < 0.001, p = 0.001, p = 0.002, p = 0.01 respectively). Finally, a positive correlation was found between CIMT (right) and RWT (p = 0.01).

Table 8
Correlations of pulse wave analysis parameters with ECHO and CIMT measurements

	IVSDd		LVEDd		LVPWd		LVmass		LVmass index		RWT		CIMT(right)		CIMT(left)	
	r	P	r	p	r	p	r	p	r	p	r	p	r	p	r	p
SBP (mmHg)	0.48	**< 0.001**	0.11	0.35	0.41	**< 0.001**	0.39	**0.001**	0.22	0.06	0.31	**0.007**	-0.30	0.8	-0.05	0.63
DBP (mmHg)	0.29	**0.01**	0.13	0.26	0.31	**0.008**	0.26	**0.02**	0.35	**0.002**	0.19	0.1	-0.03	0.77	0.02	0.83
MAP (mmHg)	0.44	**< 0.001**	0.12	0.30	0.41	**< 0.001**	0.37	**0.001**	0.32	**0.006**	0.31	**0.009**	-0.03	0.78	-0.04	0.69
HR (beat/min)	-0.08	0.5	-0.16	0.17	-0.2	0.08	-0.18	0.11	-0.22	0.06	-0.17	0.15	0.17	0.13	0.02	0.85
PP (mmHg)	0.37	**0.001**	0.06	0.59	0.29	**0.01**	0.33	**0.005**	0.0	0.99	0.25	**0.03**	0.02	0.85	-0.03	0.78
cSBP (mmHg)	0.5	**< 0.001**	0.12	0.31	0.41	**< 0.001**	0.4	**< 0.001**	0.27	**0.02**	0.31	**0.008**	0.06	0.61	0.03	0.79
cDBP (mmHg)	0.3	**0.009**	0.12	0.38	0.3	**0.01**	0.27	**0.02**	0.35	**0.002**	0.21	0.07	0.008	0.95	-0.01	0.89
AIx (%)	-0.12	0.28	0.26	**0.02**	-0.21	0.07	-0.29	**0.01**	-0.13	0.25	-0.14	0.24	0.27	**0.02**	0.22	**0.05**
PR (s.mmHg/ml)	0.06	0.61	-0.13	0.27	0.10	0.38	-0.48	0.69	0.20	0.09	0.14	0.22	0.10	0.36	0.19	0.09
RM (%)	0.03	0.76	-0.09	0.44	-0.06	0.57	-0.07	0.53	0.03	0.75	-0.05	0.65	0.31	**0.007**	0.29	**0.01**
PWV (m/sec)	0.41	**< 0.001**	0.17	0.13	0.38	**0.001**	0.36	**0.002**	0.21	0.07	0.28	**0.01**	-0.15	0.2	-0.2	0.08
CIMT(right)	0.19	0.1	0.03	0.8	0.02	0.8	0.08	0.46	0.05	0.67	0.28	**0.01**	.	.	.	.
CIMT(left)	0.23	0.06	-0.05	0.66	0.11	0.35	0.05	0.65	0.10	0.38	0.08	0.47	.	.	.	.

SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, HR: heart rate, PP: pulse pressure, cSBP: central systolic blood pressure, cDBP: central diastolic blood pressure, AIx: augmentation index, PR: peripheral resistance, RM: reflection magnitude, PWV: pulse wave velocity, IVSDd: interventricular septum end-diastolic thickness, LVEDd: left ventricular end-diastolic diameter, LVPWd: left ventricular end-diastolic posterior wall thickness, LVmass: left ventricular mass, RWT: relative wall thickness, CIMT: carotid intima-media thickness. Correlations between variables with non-normal distribution were analyzed using Spearman correlation analysis.

Discussion

Childhood hypertension is an important risk factor for cardiovascular system diseases, chronic renal failure, and cerebrovascular diseases in adulthood [1]. Endothelial dysfunction and atherosclerosis are largely responsible for the development of hypertensive end organ damage. In cases who have hypertension associated with obesity and dyslipidemia, atherosclerosis findings in the aorta and coronary arteries have been reported to begin in childhood [16, 17]. In our study, the presence of early atherosclerosis and arterial dysfunction findings in hypertensive pediatric patients was investigated by examining the parameters of arterial stiffness and CIMT.

In the present study, the BMI of obese hypertensive children was found to be higher compared to primary and renal hypertensive patients and healthy controls. However, peripheral and central blood pressure values were similar to other patients and healthy children. It has been reported that obese children have higher mean systolic and diastolic blood pressure levels in comparison to those with normal weight [18, 19]. Moore et al. [20] found a relationship between increased BMI and high blood pressure in children. Sorof et al. [21] found the rate of hypertension to be 2–3% among children with normal BMI and 11% among those with BMI ≥ 95th percentile. The lack of a significant difference in blood pressure values in obese hypertensive children despite high BMI values may be related to the low mean age of our patients and the low number of subjects. Also, 44.4% of the patients in the OPH group were receiving antihypertensive treatment and strict diet control, resulting in an increased number of patients whose blood pressure values are under control. But, although the rate of antihypertensive drug use was higher in the PH and RH groups, peripheral MAP and cSBP values in both groups, and additionally peripheral SBP, DBP, and cDBP values in the PH group were higher compared to healthy children. Regarding the higher blood pressure values in the PH group, it was thought that their familial tendency to hypertension and less emphasis on dietary controls due to their normal BMI values may have played a role in the detection of higher blood pressure values in those children. However, in hypertension due to chronic renal diseases, blood pressure control is very difficult and often requires multiple antihypertensive therapy [22].

Pulse wave analysis by the oscillometric method is a very useful and reliable method in the evaluation of arterial stiffness especially in adults, and its use in children is becoming increasingly common. In children with hypertension, especially in the presence of obesity, the increase in PWV supports the increase in arterial stiffness [7–9, 23]. Meng et al. [24] examined hypertensive and normotensive children and found PWV to be higher in the hypertensive group. Kulsum-Mecci et al. [9] compared normotensive obese, hypertensive, and hypertensive obese children with a healthy control group and found PWV to be significantly higher in all patient groups than the control group. They also stated that PWV increased with age and did not differ according to sex or race. Sakuragi et al. [25] reported that PWV showed a significant positive correlation with BMI, body fat ratio, and waist circumference in children. Dangart et al. [26] found a higher increase in PWV and DBP in obese children compared to controls at the end of a 5-year follow-up. Niboshi et al. [27] found that age, blood pressure, and heart rate were key determinants of PWV in healthy Japanese children, although obesity and PWV did not correlate.

The augmentation index is another frequently used measure of arterial stiffness along with PWV (28). Although increased AIx values has been associated with target organ damage such as left ventricular hypertrophy and increased intima-media thickness in the arteries in adults, long-term studies are not yet available in children [29, 30]. The fact that the shorter aortic length in young children causes the reflected wave to return early causes AIx to decrease gradually with age [29]. Wójtowicz et al. [31] compared obese/overweight children with or without primery hypertension with a healthy control group and reported that obese children with arterial hypertension showed the highest values of PWV, with no difference in terms of AIx, RM, or PR. Tokgöz et al. [32] reported that PWV and AIx were higher in children with primary and white coat hypertension compared to healthy controls and this was associated with the duration of hypertension. In our study, there was no statistically significant difference between the groups in terms of arterial stiffness parameters such as AIx, RM, PR, and PWV ($p > 0.05$). No correlation was found between duration of hypertension and PWV, AIx, RM, or CIMT. However, in accordance with the literature, PWV was positively correlated with height, weight, BMI, SBP, DBP, MAP, PP, cSBP, and cDBP; AIx was negatively correlated with age, height, and weight and positively correlated with DBP, MAP, HR, and cDBP. Also, CIMT values were positively correlated with AIx and RM. In our study, most of the patients were diagnosed with hypertension recently, which suggests that exposure to high blood pressure was short-lived. Besides, the low mean age of our study group and the low number of subjects might have been effective in the lack of difference in terms of endothelial damage findings and the lack of correlation between duration of hypertension and atherosclerosis markers.

Measurement of central (aortic) blood pressure in hypertensive patients has gained more importance as it gives a clearer idea about cardiovascular events than peripheral (arm) measurement. Central blood pressure is more sensitive in evaluating target organ damage and response to antihypertensive therapy, since central blood pressure directly affects the organs and peripheral blood pressure does not always reflect central blood pressure [33]. Litwin et al. [34] found central blood pressure to be normal in all patients with white coat hypertension and in 93% of the prehypertensive group. In the severe hypertension group, mean cSBP, PP, PWV, and the prevalence of left ventricular hypertrophy was found to be significantly higher than in children with white coat hypertension, prehypertensive, and hypertensive children. They also found that LVmass index and CIMT correlated with both cSBP and PP. Totaro et al. [35] found CIMT, LVmass, AIx, and PWV to be higher in normotensive cases with high central blood pressure. In our study, there was no significant correlation between LVmass index and peripheral SBP, but a significant positive correlation with cSBP ($p = 0.02$). Moreover, a positive correlation was found between both peripheral and central DBP and LVmass index ($p = 0.002$). This finding supports that central blood pressure values may be more significant than peripheral measurements for determining target organ damage due to hypertension in hypertensive pediatric patients, as in adult patients.

Hypertension is an important risk factor for atherosclerosis. Especially in patients with additional risk factors such as diabetes, hyperlipidemia, and obesity, endothelial dysfunction caused by hypertension considerably increases the risk of developing atherosclerosis. Pathological studies have shown that atherosclerosis begins in childhood and continues, and fatty streaks can be observed in the coronary and carotid arteries of children and adolescents [36, 37]. Lande et al. [38] reported that CIMT was increased in hypertensive children and was correlated with SBP. Di Salvo et al. [39], Morrison et al. [40], and Pandit et al. [41] found that CIMT did not differ between normotensive obese children and healthy controls. Similarly, we found no statistical difference between the groups in terms of CIMT, despite including non-obese primary hypertensive patients and those with additional risk factors like obesity and chronic renal disease ($p > 0.05$). Also, CIMT measurements were not significantly correlated with blood pressure parameters or anthropometric measurements. This was again associated with the low mean age of our patients and the fact that hypertension was under control.

Cardiac remodeling caused by hypertension is the most prominent form of target organ damage and is associated with increased cardiovascular mortality and morbidity. It has been shown that increased left ventricular mass and concentric hypertrophy in hypertensive adult patients increase the risk of cardiovascular events [42]. DeSimone et al. [43] reported that the risk of cardiovascular events increased fourfold if the LVmass index was above 51 $gr/m^{2.7}$. Although hypertension-related left ventricular hypertrophy can be seen in children, it is more common, particularly in late adolescent and young adult age groups [44, 45]. Celik et al. [46] found LVEDd, IVSDd, LVPWd, and LVmass indexes to be significantly higher in obese children compared to the controls. Sorof et al. [47] found that LVmass index showed a strong correlation with ambulatory systolic blood pressure but not with age, weight, or ambulatory DBP in 37 untreated hypertensive children. Di Bonito et al. [48], on the other hand, found that high blood pressure, rather than BMI, was an independent predictor of concentric left ventricular hypertrophy in children. In our study, IVSDd and LVmass were statistically significantly increased in the OPH group compared to the control group ($p = 0.02$ and $p = 0.016$, respectively). There was no statistically significant difference between the groups in terms of LVmass index and RWT. The fact that IVSDd was statistically significantly higher ($p = 0.014$) in the RH group as well as OPH group than the control group suggests the potential role of the pressure overload effect of hypertension, along with hypertrophy caused by obesity, in the formation of cardiac target organ damage. Besides, despite the lack of a significant correlation between LVmass index and BMI, high blood pressure is considered a more important predictor of left ventricular hypertrophy than BMI, since LVmass index was positively correlated with peripheral diastolic and mean blood pressures, PP, or central systolic and diastolic blood pressures.

Various risk factors such as smoking, hypertension, and hyperlipidemia initiate an inflammatory response by disrupting the endothelial structure. C-reactive protein is a parameter used to assess inflammation and is a risk factor for cardiovascular events and increased arterial stiffness [49]. The National Health and Nutrition Examination Survey showed that adiposity and high SBP were associated with CRP [50, 51]. Noronha et al. [52] found that CRP was associated with obesity and high blood pressure in children. Rondò et al. [53] reported that CRP was positively correlated with SBP and waist circumference and negatively correlated with HDL-C levels. Mohamed et al. [54] found that CRP was positively correlated with BMI but not with blood pressure values. In our study, however, no correlation was found between CRP and blood pressure, pulse wave analysis parameters, or CIMT values, except for a weak negative correlation with peripheral and central DBP values.

In humans, uric acid is the main product of the catabolism of purine nucleotides (adenosine and guanosine). Hyperuricemia is associated with hypertension, vascular disease, renal disease, and cardiovascular events. The Bogalusa Heart Study [55], the Moscow Pediatric Hypertension Study [56], and the 3rd National Health and Nutrition Examination Survey [57] reported that serum uric acid levels are associated with hypertension in children. In our study, however, there was no statistically significant difference between the groups in terms of serum uric acid values. But, serum uric acid values were found to be positively

correlated with peripheral SBP, PP, and PWV values (p = 0.009, p = 0.001, p = 0.02, respectively) and negatively correlated with AIx (p = 0.001). This finding suggests that, even when uric acid values are not high, they might be correlated with pulse wave analysis parameters.

Urinary albumin excretion reflects glomerular permeability and increased urinary albumin excretion is indicative of increased renal damage [58]. Microalbuminuria is associated with early target organ damage, left ventricular hypertrophy, and increased CIMT in nondiabetic hypertensive patients [59]. Parving et al. [60] reported that microalbuminuria was significantly increased in non-diabetic patients with primary hypertension compared to controls. Nguyen et al. [61] found a significant relationship between hypertension and microalbuminuria in obese adolescents. On the other hand, Göknar et al. [62] found no difference in terms of microalbuminuria between obese children and healthy controls. Similarly, we found no statistically significant difference between the groups in terms of microalbumin/creatinine in spot urine and microalbumin/creatinine ratio was not correlated with any of the study parameters. Considering that the urine samples were studied at different times of the day, the fact that we could not exclude factors like orthostatic proteinuria may have led to the lack of difference between the groups.

Dyslipidemias are known to play a role in cardiovascular events such as hypertension and obesity in adults. There is evidence indicates that high serum total cholesterol, LDL-C, glucose, and insulin levels in childhood are associated with atherosclerotic outcomes in young adults [63–66]. Bjelakovic et al. [67] found that triglyceride/HDL-C ratio was positively correlated with eccentric left ventricular hypertrophy and both BMI and insulin levels were positively correlated with concentric left ventricular hypertrophy in obese children. Sierakowska-Fijalek et al. [68] found statistically significantly higher serum LDL-C, total cholesterol and triglyceride, and lower serum HDL-C levels in children with atherosclerosis risk factors compared to healthy controls. Raitakari et al. [69] stated that adult CIMT was associated with childhood LDL-C, SBP, and BMI. In our study, serum fasting glucose levels were positively correlated with PP and CIMT right (p = 0.002, p = 0.03, respectively). Also, serum insulin levels were found to correlate with SBP, MAP, PP, cSBP, PWV, IVSDd, LVEDd, LVPWd, LVmass, and RWT (p < 0.001, p = 0.02, p < 0.001, p < 0.001, p = 0.007, p = 0.001, p = 0.05, p = 0.002, p = 0.01, p = 0.05, respectively). Moreover, homa-IR was positively correlated with SBP, MAP, PP, cSBP, PWV, IVSDd, LVPWd, LVmass, and RWT (p < 0.001, p = 0.02, p < 0.001, p < 0.001, p = 0.007, p = 0.001, p = 0.003, p = 0.002, p = 0.05, respectively). However, no correlation was found between serum HDL-C, LDL-C, and triglyceride levels with ECHO parameters or pulse wave analysis parameters. The correlations of PWV with homa-IR and insulin levels supports that insulin resistance is a predictor of subclinical vascular damage and future cardiovascular events.

In conclusion, the ambulatory 24-hour pulse wave analysis by the oscillometric method revealed that children with primary hypertension had higher SBP, DBP, MAP cSBP, and cDBP values and those with renal hypertension had higher MAP and cSBP values compared to healthy controls. Especially, the positive correlations of central blood pressure values with PWV, AIx, and BMI supports that hypertension has a key role in the formation of arterial stiffness and that obesity is associated with blood pressure and arterial stiffness. LVmass index was found to have no significant correlation with peripheral SBP, although its significant positive correlation with cSBP and cDBP supports that central blood pressure is a better predictor of target organ damage. We believe that using pulse wave analysis and central blood pressure measurement to determine deterioration in arterial structure and functions due to hypertension, is an effective and reliable method in children. This can help prevent the development of cardiovascular disease and target organ damage by enabling necessary lifestyle measures to be taken.

Declarations

Conflict of interest

The authors declare no competing interests.

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