

Assessment of Early Cardiovascular Risk in Children and Adolescents with Essential Hypertension

Bewertung des kardiovaskulären Risikos bei Kindern und Jugendlichen mit essentieller Hypertonie

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adipokines, essential hypertension, intima-media thickness, left ventricular hypertrophy, pulse wave velocity

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Bibliography

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ABSTRACT

Objectives The aim of our study was to investigate some early markers of hypertensive target organ damage in hypertensive children and adolescents, and to detect those showing most prominent clinical significance.

Methods We included 100 children with essential hypertension (EH) and 50 age-matched healthy control children, and evaluated left ventricular mass (LVM), intima-media thickness in the carotid arteries (IMT), pulse wave velocity (PWV), microalbuminuria, biochemical parameters and some adipokines.

Results Statistically significant differences between the 2 groups were observed for HDL-cholesterol, LDL-cholesterol, triglycerides, insulin, uric acid, glucose, apolipoprotein A1, and total adiponectin. The mean values of IMT, PWV and LVM were greater in hypertensive children, but only the differences in IMT and LVM were statistically significant. In addition, hypertensive children showed significantly higher values of AoSP (aortic systolic pressure), AoPP (aortic pulse pressure) and Alx@75 (augmentation index corrected for heart rate of 75 b.p.m.). Metabolic syndrome was diagnosed in 31 % of hypertensive children.

Conclusions A significant number of children with EH have early target organ changes as well as other risk factors, including metabolic syndrome, especially obese ones. However, IMT, LVM and some parameters of arterial stiffness have been found to be early markers in both obese and non-obese hypertensives. In addition, adipokines and coagulation factors seem to be important in obese hypertensives.

ZUSAMMENFASSUNG

Hintergrund Das Ziel unserer Studie war es, einige frühe Zeichen hypertensiver Endorganschäden bei Kindern und Jugendlichen mit arterieller Hypertonie zu ermitteln um diejenigen zu finden, die klinisch am bedeutsamsten sind.

Patienten Wir haben 100 Kinder und Jugendliche mit essentieller Hypertonie (EH) und 50 gleichaltrige gesunde Kinder und Jugendliche als Kontrollen in die Studie einbezogen.

Methoden Die Studie beurteilte die linksventrikuläre Hypertrophie (LVM), die Intima Media Dicke der inneren Halsschlagader (IMT), die Pulswellengeschwindigkeit (PWV), Mikroalbuminurie, einige biochemische Parameter und Adipokine.

Ergebnisse Zwischen den 2 Gruppen fanden wir statistisch signifikante Unterschiede für das HDL-Cholesterin, LDL-Cholesterin, die Triglyceride, das Insulin, die Harnsäure, den Blutzucker, das Apolipoprotein A1 und das Gesamt-Adiponectin. Die Mittelwerte (Durchschnittswerte) von IMT, PWV und LVM waren höher bei hypertensiven Kindern, aber nur die Unterschiede von IMT und LVM waren statistisch bedeutsam. Außerdem zeigten die hypertensiven Kinder signifikant höhere Werte vom AoSP (systolischer Druck in der Aorta), AoPP (Pulsdruck in der Aorta), und Alx@75 (Augmentations-Index adaptiert an die Herzfrequenz von 75/min). Das metabolische Syndrom haben wir bei 31 % der hypertensiven Kinder diagnostiziert.

Schlussfolgerung Eine signifikante Anzahl von Kindern mit EH, insbesondere die Übergewichtigen, haben frühe Endorgan-schäden sowie auch andere Risikofaktoren einschließlich des Metabolischen Syndroms. Allerdings haben sich IMT, LVM und einige Parameter der Arteriensteifigkeit als frühe Zeichen in

beiden Gruppen, sowohl bei den Übergewichtigen, als auch bei Kindern mit Normalgewicht, erwiesen. Des Weiteren scheinen bei hypertensiven Übergewichtigen Adipokine und Gerinnungs-faktoren von Bedeutung zu sein.

Introduction

The frequency of arterial hypertension (AH) in 8–18 year-old children is about 2.0–3.6% and almost 10% among 18 years old adolescents [1, 17]. It is known to be one of the most important factors for the development of atherosclerosis and represents the main risk factor for cardiovascular disease in adults [29]. 2 of the important aspects of the management of hypertensive children are the detection of early changes of hypertensive target organ damage and assessment of the total cardiovascular risk of the individual patient [22]. With the obesity epidemic, AH has become one of the most common chronic diseases in adolescence [17]. It has been proposed that traditional risk factors must be considered in the evaluation of children with elevated blood pressure (BP) [22]. However, in recent years, increasing amounts of data have stressed the importance of newer risk factors for atherosclerosis, such as homocysteine, lipoprotein (a), apolipoprotein B, adipokines and markers of fibrinolysis and inflammation [11, 13, 14, 16, 17, 21]. In addition, studies have been performed in these children to investigate early markers of target organ damage such as increased carotid intima-media thickness (IMT) [9, 20], higher pulse wave velocity (PWV) [27] and left ventricular hypertrophy [2, 8, 18]. Other studies have discussed additional atherosclerotic risk factors in hypertensive children and adolescents, but none to the extent investigated in our study.

With respect to these facts, the aim of our study was to investigate some early markers of hypertensive target organ damage and to detect those hypertensive children who might be at greater risk of developing cardiovascular diseases.

Materials and Methods

The study cohort consisted of 100 patients (50 girls and 50 boys) with untreated essential hypertension diagnosed according to the diagnostic criteria [23]. In addition, the hypertension was confirmed with pathologic 24-h ambulatory BP monitoring using height and sex specific reference values [23]. The mean age of the patients was 15.3 ± 2.8 years (range 5–20 years).

The control group consisted of 50 healthy children of comparable gender and age with normal BP and without any other cardiovascular risk factors (26 girls and 24 boys) with a mean age of 15.3 ± 3.1 years (range 5–20 years).

An informed consent was obtained from all patients or their parents, and the study was approved by the state medical ethics committee (KME 121/11/08).

Our study was a cross-sectional study. In each individual, a detailed clinical examination was carried out, and the patients' medical history was evaluated. Body weight and height were recorded and body mass index (BMI) was calculated. BP levels were assessed according to the recommendations of the Fourth Report on the Di-

agnosis, Evaluation, and Treatment of High blood pressure in Children and Adolescents [23]. Hypertension was defined as an average systolic or diastolic BP greater than 95th for age, gender and height on at least 3 separate occasions. In cases of hypertension, BP was confirmed by 24-h ambulatory BP measurement (ABPM) using a Space Labs 90207 device. The data published by Soergel et al. were used as the reference values for ABPM [28].

The mean value of the average whole day systolic BP in hypertensive children, confirmed by 24-h ABPM was 134.0 ± 5.9 mmHg, the average diastolic BP 73.5 ± 6.1 mmHg, the mean day systolic 137.0 ± 5.8 mmHg, the mean day diastolic BP 76.0 ± 6.5 mmHg, the mean night systolic BP 129 ± 7.6 mmHg and the mean night diastolic BP 70.0 ± 6.9 mmHg.

Essential hypertension (EH) was diagnosed after a thorough clinical and laboratory diagnostic work-up that closely followed recently published recommendations [23]. Blood was taken in the fasting state between 8.00–10.00 am to determine lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides), apolipoprotein A and B, lipoprotein (a), uric acid, glucose, insulin, homocysteine, C-reactive protein (CRP), fibrinogen and plasminogen activator inhibitor-1 (PAI-1), using standard procedures. A spot urine was obtained at the same time to assess microalbuminuria.

The level of total adiponectin and leptin in the blood was determined using the quantitative sandwich enzyme immunoassay technique and of ghrelin using the sandwich ELISA method.

A Toshiba Aplio XU ultrasonoscope with a 5–10 MHz linear probe was used to investigate the carotid arteries (point to point measurement). IMT was measured at 2 different sites of the left and the right carotid artery in the region of the common carotid artery (up to 1 cm below the bifurcation) [24]. At each site, 2 measurements were taken and the average was calculated. We used official recommendations for IMT measurement in youth published by Pignoli et al. in 1986 [24] and by Urbina et al. in 2009 [30] and compared our measurements with normal values published by Urbina et al. 2009 [30].

Arterial stiffness was determined by applanation tonometry using the Sphygmo Cor PX device interfaced with a computer. Aortic PWV, measured by sequential recordings of the arterial pressure wave at the carotid and radial arteries, was defined as the distance of the sampling sites divided by the time difference between the rise delay of the distal and proximal pulse according to the R wave belonging to the electrocardiogram (ECG) QRS complex and calculated by the software. To assess pulse wave travel distance, surface tape measurements were performed between the carotid site and the jugular notch and between the jugular notch and the radial site. The difference between these 2 distances was considered as the pulse travel distance in m/s [7]. We compared our measurements with normal values published by Reusz et al. in 2010 [26].

Echocardiography was performed using a Toshiba Aplio XU ultrasonoscope allowing M-mode, 2-dimensional and pulsed Doppler measurements. To standardize left ventricular mass to height, we calculated left ventricular mass (LVM) using the deSimone formula [10]. According to the recommendations of Khoury et al., published in 2009, left ventricular hypertrophy for children aged >9 years was defined as a value above $40 \text{ g/m}^{2.7}$ (cut-off for the 95th percentile) for girls and $>45 \text{ g/m}^{2.7}$ for boys. For patients aged <9 years, the index varies with age, and therefore, measured LVM/height (2.7) was compared with percentile curves provided by Khoury et al. [15].

Statistics

Statistical analysis was performed using basic statistical methods. Data distribution was calculated using the Kolmogorov-Smirnov test of normality. A bivariate analysis of anthropometric, laboratory and morphological data between the study and the control group was performed using Fisher's exact test to compare the categorical data. The independent samples t-test was used to compare the numerical data between groups. In case normal distribution was not given, the Mann-Whitney U test was used. A bivariate analysis of anthropometric, laboratory and morphological data according to BMI was performed using an independent samples t-test or the Mann-Whitney U test for parameters without normal distribution. A nonparametric Spearman's rho test was used to calculate correlations of IMT, PWV and LVM with laboratory data.

The level of significance was set at $p < 0.05$. Statistical analysis was carried out using IBM SPSS 22.0 (IBM Corp., Armonk, NY).

Results

The anthropometric characteristics of our subjects are shown in ► **Table 1**. No statistically significant differences were found in age and gender, but there were statistically significant differences in weight, BMI, waist circumference, hip circumference and waist/hip proportion.

There were also no statistically significant gender differences between normal weight (51 % men and 49 % women) and overweight hypertensive (49 % men and 51 % women) children.

We found no statistically significant differences between the BMI of normal weight hypertensive children and the BMI of the control group ($p = 0.12$).

Differences in clinical, laboratory and morphologic parameters between normal weight, overweight and obese hypertensive children are shown in ► **Table 2**.

► **Table 3** shows the differences in laboratory findings between the hypertensive and control group of children. Statistically significant differences between the 2 groups were observed for HDL cholesterol, triglycerides, insulin, uric acid, glucose and apolipoprotein A1. However, when comparing only the normal weight hypertensive children of the study group with the control group, a significant difference was found only for glucose (► **Table 3**).

The percentages of pathological values of some laboratory findings are shown in ► **Fig. 1**.

The mean values of IMT, PWV, LVM, left ventricular (LV) posterior wall thickness and interventricular septum thickness were greater in hypertensive children compared to the control group, but only the differences in IMT ($p < 0.001$), LVM ($p < 0.001$), left ventricular (LV) posterior wall thickness ($p < 0.001$) and interventricular septum thickness ($p = 0.003$) were statistically significant, whereas PWV was not. We found statistically significant differences in some morphological parameters (IMT, AoSP, AoPP, interventricular septum thickness and LVM) between normal weight hypertensive children and the control group (► **Table 4**).

Comparing our IMT measurements with normal values for children and adolescents published by Urbina in 2009, pathological values of IMT were found in 37 % of the hypertensive group.

The PWV measurements were compared with normal values for children and adolescents published by Reusz in 2010. 56 % of hypertensive children reached values over the 90th percentile.

The differences in adipokines between the study and the control group are presented in ► **Table 4**.

No statistically significant differences between the 2 groups were observed for microalbuminuria ($p = 0.744$).

We also performed a correlation analysis of all laboratory parameters with IMT, PWV and LVM. Positive correlations were found for IMT and uric acid ($r = 0.38$, $p < 0.001$), PAI-1 ($r = 0.26$, $p = 0.009$), insulin ($r = 0.24$, $p = 0.016$), adiponectin ($r = 0.25$, $p = 0.012$) and HDL-cholesterol ($r = 0.21$, $p = 0.036$). The correlation between laboratory parameters and PWV was positive for total cholesterol

► **Table 1** Anthropometric characteristics of the study subjects and the control group [Mean values \pm SD].

Characteristics	Study group (n = 100)	Control group (n = 50)	p
Age [y]	15.3 \pm 2.8	15.3 \pm 3.1	n. s.
Sex (M/F) [N(%)]	50 (50%)/50 (50%)	24(48%)/26(52%)	n. s. *
Weight [kg] (z)	77.5 \pm 21.1 (1.9 \pm 1.8)	59.1 \pm 15.1 (0.3 \pm 0.7)	<0.001 **
Systolic BP (mmHg)	140.9 \pm 10.3	113.2 \pm 8.2	<0.001
Diastolic BP (mmHg)	81.5 \pm 9.7	67.6 \pm 6.1	<0.001
BMI [kg/m ²] (z)	26.4 \pm 5.8 (3.1 \pm 3.0)	20.7 \pm 2.5 (0.1 \pm 0.9)	<0.001 **
Waist [cm] (z)	88.9 \pm 16.0 (3.0 \pm 2.4)	76.7 \pm 10.0 (1.3 \pm 1.3)	<0.001 **
Hip [cm] (z)	102.7 \pm 16.2 (1.8 \pm 1.9)	96.1 \pm 11.1 (1.1 \pm 1.0)	0.037 **
Waist/hip proportion [%] (z)	0.86 \pm 0.09 (0.8 \pm 1.1)	0.80 \pm 0.07 (0.1 \pm 0.7)	<0.001 **

The values in parentheses denote the z-score; When z-scores were denoted then p value was calculated for z-scores; BMI: body mass index, BP: blood pressure, n. s.: not significant, N: number, y: years; Statistical test: p: independent samples t-test; p*: Fisher's exact test; p**: Mann-Whitney U test

► **Table 2** Differences in clinical, laboratory and morphologic parameters between normal weight, overweight and obese children in the study group [Mean values ±SD].

Parameters	BMI ≤90 Percentile (n=45)	90> BMI <97 Percentile (n=20)	BMI ≥97 Percentile (n=35)	p1	p2	p3
Weight [kg] (z)	63.2±11.6 (0.4±0.7)	74.5±19.8 (1.7±0.4)	93.6±18.0 (3.5±1.6)	<0.001 *	<0.001 *	<0.001 *
Waist circumference [cm] (z)	77.6±8.0 (1.2±1.1)	87.3±11.4 (2.4±1.2)	101.4±14.7 (4.9±2.3)	0.003 *	<0.001 *	<0.001 *
Hip circumference [cm] (z)	93.0±8.4 (0.6±0.8)	98.3±13.7 (1.5±1.2)	114.7±15.8 (3.3±1.9)	0.002 *	<0.001 *	0.001 *
Waist/hip proportion [%] (z)	0.83±0.07 (0.5±0.8)	0.89±0.08 (0.7±0.9)	0.89±0.10 (1.2±1.3)	n. s. *	0.001 *	n. s. *
IMT right side [mm]	0.42±0.09	0.41±0.07	0.46±0.09	n. s.	0.018	0.014
IMT left side [mm]	0.42±0.08	0.41±0.05	0.46±0.08	n. s.	0.022	0.018
Left ventricular posterior wall thickness [mm]	11.0±2.4	11.0±2.3	12.4±2.9	n. s.	0.011	0.016
Uric acid [μmol/l] (z)	266.3±58.4 (-0.5±1.0)	282.5±65.1 (0.0±0.9)	320.6±68.2 (0.6±1.3)	n. s. *	<0.001 *	n. s. *
HDL cholesterol [mmol/l] (z)	1.5±0.3 (2.0±2.5)	1.4±0.3 (0.3±2.2)	1.2±0.3 (-0.3±2.2)	n. s. *	<0.001 *	n. s. *
LDL cholesterol [mmol/l] (z)	2.3±0.7 (-0.1±1.3)	2.7±0.7 (0.3±1.5)	2.8±0.8 (1.0±1.8)	n. s. *	0.002 *	n. s. *
Triglycerides [mmol/l] (z)	0.9±0.5 (0.3±3.0)	1.2±0.8 (2.2±3.7)	1.4±0.7 (3.8±4.6)	n. s. *	<0.001 *	n. s. *
Insulin [μU/ml] (z)	12.3±6.8 (1.4±2.6)	14.7±9.7 (2.7±3.7)	22.6±12.5 (5.0±4.5)	n. s. *	<0.001 *	0.048 *
Apolipoprotein B [g/l] (z)	0.7±0.2 (-1.2±1.3)	0.8±0.2 (-1.0±1.1)	0.8±0.2 (0.1±1.8)	n. s. *	0.001 *	n. s. *
Fibrinogen [g/l] (z)	3.0±0.7 (1.0±1.4)	2.7±0.4 (0.0±1.1)	3.4±0.9 (1.6±1.7)	=0.029 *	n. s. *	0.003 *
PAI-1 [U/ml] (z)	1.5±1.3 (-1.4±0.6)	2.2±1.8 (-0.8±1.1)	2.6±2.0 (-1.0±0.9)	n. s. *	n. s. *	n. s. *
Adiponectin [ng/ml]	81.9±44.0	70.3±34.1	47.4±25.7	n. s. *	<0.001 *	n. s. *
Leptin [pg/ml]	62.3±53.8	102.2±121.1	165.7±105.3	n. s. *	<0.001 *	n. s. *
Ghrelin [pg/ml]	653.3±306.2	624.9±320.6	499.2±256.3	n. s. *	0.044 *	n. s. *

p1: BMI ≤ 90 vs. BMI 90<BMI<97, p2: BMI ≤ 90 vs. BMI ≥ 97, p3: BMI 90<BMI<97 vs. BMI ≥ 97; The values in parentheses denote the z-score. When z-scores were denoted then p value was calculated for z-scores; HDL: high density lipoprotein, IMT: intima media thickness, LDL: low density lipoprotein., n.s.: not significant, PAI-1: plasminogen activator inhibitor-1; Statistical test: p: independent samples t-test; p*: Mann-Whitney U test

► **Table 3** Laboratory findings for the hypertensive and control groups [Mean values ±SD].

Laboratory parameters	CG (n=50)	SG1 (n=100)	p1	SG2 (n=45)	p2
Total cholesterol [mmol/l] (z)	4.2±0.7 (0.4±1.6)	4.2±1.0 (0.6±2.5)	n. s. *	4.0±0.9 (0.1±1.6)	n. s. *
HDL cholesterol [mmol/l] (z)	1.5±0.3 (1.7±2.4)	1.4±0.3 (0.8±2.5)	0.026 *	1.5±0.3 (2.0±2.5)	n. s. *
LDL cholesterol [mmol/l] (z)	2.3±0.7 (-0.2±1.5)	2.6±0.8 (0.4±1.6)	n. s. *	2.3±0.7 (-0.1±1.3)	n. s. *
Triglycerides [mmol/l] (z)	0.8±0.3 (0.3±1.9)	1.2±0.7 (2.0±4.1)	0.043 *	0.9±0.5 (0.3±3.0)	n. s. *
Glucose [mmol/l] (z)	4.5±0.5 (-1.2±0.9)	4.7±0.5 (-0.8±0.9)	0.024 *	4.8±0.5 (-0.8±0.9)	0.036 *
Insulin [μU/ml] (z)	9.9±3.3 (0.4±1.2)	16.9±11.0 (3.1±4.0)	<0.001 *	12.2±6.8 (1.4±2.6)	n. s. *
Uric acid [μmol/l] (z)	254.8±62.2 (-0.6±1.4)	291.2±67.9 (0.1±1.2)	0.001 *	266.6±59.3 (-0.5±1.0)	n. s. *
Homocysteine [μmol/l] (z)	10.5±3.5 (2.7±2.1)	11.1±5.5 (2.9±3.7)	n. s. *	10.4±4.5 (2.2±2.9)	n. s. *
Apolipoprotein A1 [g/l] (z)	1.5±0.3 (1.7±1.9)	1.4±0.2 (0.9±1.8)	0.015 *	1.5±0.2 (1.2±1.7)	n. s. *
Apolipoprotein B [g/l] (z)	0.7±0.2 (-1.0±1.4)	0.7±0.2 (-0.6±1.6)	n. s. *	0.7±0.2 (-1.2±1.3)	n. s. *
Lipoprotein [a] [g/l] (z)	0.2±0.2 (1.9±4.3)	0.2±0.2 (1.9±4.9)	n. s. *	0.1±0.2 (1.0±3.5)	n. s. *
Fibrinogen [g/l] (z)	3.1±0.8 (1.1±1.7)	3.1±0.8 (1.2±1.6)	n. s. *	3.0±0.7 (1.0±1.4)	n. s. *
PAI-1 [U/ml] (z)	1.6±1.8 (-1.3±0.9)	2.1±1.7 (-1.1±0.8)	n. s. *	1.5±1.3 (-1.4±0.6)	n. s. *
CRP [mg/l] (z)	3.8±3.0 (0.2±1.9)	3.6±2.8 (0.1±1.8)	n. s. *	3.0±1.1 (-0.3±0.7)	n. s. *

CG: control group, SG1: study group, SG2: study group (BMI ≤ 90 percentile); p1: SG1 vs. CG, p2: SG2 vs. CG; The values in parentheses denote the z-score. When z-scores were denoted then p value was calculated for z-scores; CRP: C reactive protein, HDL: high density lipoprotein, LDL: low density lipoprotein, n. s.: not significant, PAI-1: plasminogen activator inhibitor-1; Statistical test: p: independent samples t-test; p*: Mann-Whitney U test

($r=0.24$, $p=0.018$) and uric acid ($r=0.23$, $p=0.025$). For LVM only positive correlation with adiponectin was found ($r=0.22$, $p=0.028$).

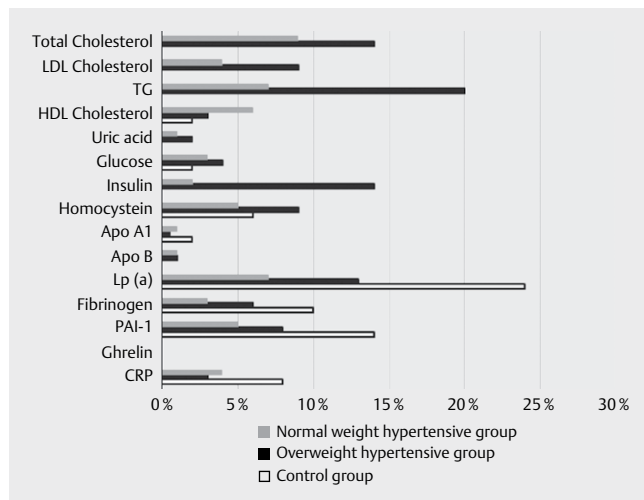
Metabolic syndrome was detected only in hypertensive children, with 31 % of the hypertensive children fulfilling the criteria for the

metabolic syndrome; 14% had 4 criteria and almost 3% had 5 criteria for the metabolic syndrome. There were no children with metabolic syndrome in normal weight hypertensives.

Discussion

Hypertension is a cardiovascular risk factor in both children and adults. In addition, a lot of patients with hypertension have other cardiovascular risk factors such as obesity and high cholesterol [13, 17].

There is growing evidence that the presence of multiple risk factors is associated with striking evidence of an accelerated atherosclerotic process and increases the cardiovascular risk, which has been shown for adults and is also proposed for children [5].



► **Fig. 1** Pathological values of some laboratory findings for the hypertensive normal weight, overweight and control groups. Apo A1: Apolipoprotein A1, Apo B: Apolipoprotein B, CRP: C reactive protein, HDL: high density lipoprotein, LDL: low density lipoprotein, Lp (a): lipoprotein (a), PAI-1: plasminogen activator inhibitor-1, TG: triglycerides. There were no pathological values of total cholesterol, LDL cholesterol, triglycerides, uric acid, insulin and apolipoprotein B in the control group of children. There were no pathological values of ghrelin in all 3 groups.

In adults, there have been quite a few very good prospective studies investigating the connection of hypertension with cardiovascular events later in life, which is not the case in children [22]. There are no studies in pediatric patients showing that risk factors established in childhood are associated with cardiovascular disease later in life. Nevertheless, there are some studies showing that the cardiovascular risk factor presence in childhood (e. g., hypertension) is connected with higher value of the same risk factor in adulthood. The cardiovascular risk factors begin in childhood and are predictive of the cardiovascular risk in adulthood [5, 22]. The level of risk factor varies for individuals and tends to remain in a given rank over time. Tracking studies from childhood to adulthood exist for all major risk factors, showing that risk factors are tracked to various degrees, with obesity being the most tracked risk factor of all [5]. In addition, it has been shown that early hypertensive target organ changes represent the intermediate phenotype in the context of future cardiovascular events and indicate the later cardiovascular risk [22]. Many studies over the years have also indicated both that hypertension occurs more commonly among obese children than non-obese children and that obesity itself increases BP.

The aim of our study was to investigate some of the early changes in hypertensive target organs and to detect the clinically most important one. In addition, we wanted to detect the hypertensive children at greater cardiovascular risk. Therefore, we investigated whether greater IMT, LVM and PWV were present in our hypertensive children in comparison to healthy controls. In our study, these predictions were verified. Our measurements of carotid IMT, LVM and PWV were greater in the hypertensive group, but only the differences in carotid IMT and LVM were statistically significant. However, the differences in some parameters of PWV also achieved statistical significance, indicating the importance of PWV evaluation. The results are in accordance with some previously published studies [8, 18, 20]. Anyway, it has to be stressed, that most of our included hypertensive patients had grade I hypertension and the study was cross-sectional. We can speculate that even in mild hypertensive patients early changes can be detected, in the begin-

► **Table 4** IMT, LVM, PWV and some adipokines of the investigated study subjects and the control group [Mean values \pm SD].

Morphologic parameters	CG (n = 50)	SG1 (n = 100)	p1	SG2 (n = 45)	p2
IMT right side [mm]	0.35 \pm 0.05	0.43 \pm 0.09	<0.001	0.42 \pm 0.09	<0.001
IMT left side [mm]	0.36 \pm 0.05	0.43 \pm 0.08	<0.001	0.42 \pm 0.07	<0.001
PWV [m/s]	6.4 \pm 1.3	6.5 \pm 1.3	n. s.	6.6 \pm 1.3	n. s.
AoSP [mmHg]	102.2 \pm 10.2	119.9 \pm 13.9	<0.001	123.1 \pm 14.7	<0.001
AoPP [mmHg]	29.2 \pm 9.4	37.9 \pm 13.7	<0.001	39.6 \pm 15.2	<0.001
AP [mmHg]	0.4 \pm 3.4	-0.8 \pm 4.5	n. s. *	-0.3 \pm 4.3	n. s. *
Alx@HR75 [%]	3.0 \pm 10.0	0.3 \pm 11.5	0.044 *	1.5 \pm 11.3	n. s. *
Interventricular septum thickness [mm]	10.3 \pm 1.7	11.3 \pm 2.6	0.003	11.2 \pm 2.8	0.044
Left ventricular posterior wall thickness [mm]	10.2 \pm 1.7	11.5 \pm 2.6	<0.001	11.0 \pm 2.4	n. s.
LVM [g/m ^{2.7}]	31.0 \pm 6.0	37.2 \pm 11.5	<0.001	35.3 \pm 8.0	0.003
Adiponectin [ng/ml]	82.7 \pm 41.2	65.9 \pm 39.0	0.010 *	82.2 \pm 43.0	n. s. *
Leptin [pg/ml]	141.7 \pm 168.1	111.1 \pm 101.0	n. s. *	61.5 \pm 52.9	0.025 *
Ghrelin [pg/ml]	515.9 \pm 244.1	585.6 \pm 295.3	n. s. *	637.4 \pm 309.2	0.045 *

CG: control group, SG1: study group, SG2: study group (BMI \leq 90 percentile); p1: SG1 vs. CG, p2: SG2 vs. CG; Alx@HR75: augmentation index corrected for heart rate of 75 b.p.m., AoPP: aortic pulse pressure, AP: augmentation pressure, AoSP: aortic systolic pressure, IMT: intima media thickness, LVM: left ventricular mass, n. s.: not significant; Statistical test: p: independent samples t-test; p*: Mann-Whitney U test

ning of the disease. With prospective study, the importance of early changes and their progression must be confirmed.

We also compared our normal weight hypertensive children with the control group to determine the actual influence of hypertension on early target organ changes. Numerous differences in morphological parameters (IMT, AoSP, AoPP, interventricular septum thickness, LVM) between the groups have been found, which show the importance of hypertension on early changes of the cardiovascular system. Moreover, the results indicate, that hypertension per se causes early changes in vessel wall.

Many studies also demonstrated the additive effect of exposure of several cardiovascular risk factors such as obesity and insulin resistance, metabolic abnormalities and inflammation [11, 13, 14, 17, 21]. Our hypertensive children, like those in previous studies [11, 13], had statistically significant higher values of traditional cardiovascular risk factors. However, when comparing the subgroup of normal weight hypertensive children with the control group, only the difference in blood glucose was found to be statistically significant. Obesity can influence hypertension development through different mechanisms. On the other hand, there might be some common pathways of both conditions e. g., genetic ones [12, 17]. Our study clearly showed that differences in practically all classical cardiovascular laboratory risk factors exist between normal weight and overweight hypertensive patients, indicating the higher risk of obese hypertensives. Surprisingly, IMT was not statistically significantly different between the 2 groups.

Depending on diagnostic criteria, Litwin et al. estimated the prevalence of metabolic syndrome among the hypertensive children to be 15–20%, which is 10 times more frequent than in the general European pediatric population [19]. In our study, these predictions were exceeded, since 31% of our hypertensive group fulfilled the criteria for metabolic syndrome, with 14% meeting 4 criteria and 3% even meeting 5 criteria for this syndrome. Metabolic syndrome is an additional cardiovascular risk factor and an important predictor of cardiovascular risk. As metabolic syndrome was present only in obese hypertensives, the results also show higher risk of this group of children.

We also investigated some newer cardiovascular risk factors eg., uric acid, Lp (a) and microalbuminuria. Many studies have shown that Lp (a) is an early marker of cardiovascular disease and that it is higher in hypertensive adults and children [13]. However, the findings of our study were to the contrary. In the control group we found a deviation from the mean in z-score for Lp (a) possibly due to the importance of genetics in the etiology of this parameter and ethnic differences [13]. Anyway, pathological values for Lp (a) have been found only in 20% of the study group. Regarding the importance of uric acid, we confirmed the recent finding of some authors [11] but were unable to confirm the importance of homocysteine, which some studies described [13]. Interesting, there was also no difference between the 2 groups in coagulation factors, which is not in accordance with some other studies [13]. Furthermore, for many of the investigated parameters the difference, determined according to BMI, revealed that obese hypertensive patients were particularly at risk, necessitating the determination of these parameters and follow-up of this group of patients, including the coagulation factors. There is scarcity of data showing the importance of microalbuminuria in pediatric hypertension. Despite the fact it

has become a prognostic marker for cardiovascular disease in adults we found only a few studies on hypertension and microalbuminuria in childhood [4]. In our study, there were no significant differences in microalbumin between the study and the control groups. In our opinion, the reason may be found in the etiology influencing the presence of microalbuminuria, including genetics, obesity and duration and elevation of BP [4]. However, the follow-up of all parameters is proposed to finally detect clinical significance.

The influence of adipokines on BP has been thoroughly researched in adults, where lower plasma levels of adiponectin were determined in healthy individuals with prehypertension [3]. Only a few studies have been performed investigating adipokines in children with hypertension. In our study, total adiponectin was statistically significantly lower in the hypertensive group, which supports the findings of previous studies and establishes its importance as an early cardiovascular risk factor, predominantly in obese hypertensive children. The few studies on early markers in hypertensive adults also reported significant differences in other adipokines such as ghrelin and leptin, with higher values of leptin and lower values of plasma ghrelin being found [6, 25]. However, these results were not verified in our study. Moreover, the mean values were reversed. Nevertheless, in our opinion, with increasing age, these differences would become significant in our subjects. In addition, this fact might be important in obese hypertensives. Namely, we found statistically significant differences in values of all investigated adipokines between normal weight and overweight hypertensive children, as shown for adult hypertensive patients [3, 25]. According to our results, adipokines tend to be cardiovascular risk factors for overweight hypertensive children, but additional studies have to be performed to support our findings.

Conclusions

Our study showed that early target organ changes are already present in a significant number of children with EH. The most important seem to be IMT, LVM and some parameters of vessel compliance. In addition, these children, especially obese ones, often have other clinical and laboratory cardiovascular risk factors, including metabolic syndrome, indicating their greater cardiovascular risk. According to our results, follow-up measurements should be performed in future years to study the possible progress of the atherosclerotic process. In addition, adipokines and coagulation factors seem to be important in obese hypertensives.

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Contributor's Statement

All authors made a significant scientific contribution to this study. All authors are familiar with the primary data and have read the entire manuscript and take responsibility for its content. Andreja Štelcar: conception and design, morphological diagnostics, data collection analysis and interpretation, statistical analysis, writing the article. Evgenija Homšak: laboratory diagnostics, data collection analysis and

interpretation. Nataša Marčun Varda: substantial contribution to conception and design, revising the article critically for important intellectual content, final approval of the version to be published.

Conflict of Interest

The authors have no conflict of interest to disclose.

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