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Assessment of serum concentrations of matrix metalloproteinases-2, -3 and -9, and tissue inhibitor of metalloproteinases-1 in children with primary hypertension

Ocena stężeń metaloproteinaz macierzy pozakomórkowej: 2, 3, 9 oraz tkankowego inhibitora metaloproteinaz macierzy pozakomórkowej 1 w surowicy dzieci z nadciśnieniem tętniczym pierwotnym

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Abstract

Introduction: Primary hypertension is regarded to be a growing health concern in children. The pathogenesis of primary hypertension is multifactorial. The role of altered levels of matrix metalloproteinases has been proposed. In hypertension, metalloproteinases are engaged not only in vascular remodelling but also in activation of vasoconstrictive agents. **Aim of the study:** We aimed at comparing the serum concentrations of matrix metalloproteinases-2, -3 and -9, and tissue inhibitor of metalloproteinases-1 in children with primary hypertension and normotensive peers. **Materials and methods:** We surveyed 23 children with primary hypertension, aged 14.75 years (median; interquartile range, IQR 3.66) and 23 normotensive subjects, aged 14.66 years (median; IQR 6.25). Serum concentrations of matrix metalloproteinases-2, -3 and -9, and tissue inhibitor of metalloproteinases-1 were measured using enzyme-linked immunosorbent method, and the scores were compared with Mann–Whitney *U* test, with the level of significance at $p \leq 0.05$. **Results:** In children with primary hypertension, serum concentration of matrix metalloproteinase-2 [178.1 (IQR: 35.84) vs. 99.9 (IQR: 20.1) ng/mL], -3 [6.47 (IQR: 1.75) vs. 2.67 (IQR: 1.08) ng/mL], -9 [191.1 (IQR: 52.75) vs. 58.34 (IQR: 18.99) ng/mL] and tissue inhibitor of metalloproteinases-1 [863.9 (IQR: 192.9) vs. 335.41 (IQR: 109.99) ng/mL] were significantly higher than in the normotensive controls ($p < 0.00001$). Matrix metalloproteinase-9/tissue inhibitor of metalloproteinases-1 ratio [0.22 (IQR: 0.1) vs. 0.18 (IQR: 0.05)] was also significantly elevated in the hypertensive participants ($p = 0.008$). **Conclusions:** Elevated serum concentrations of matrix metalloproteinases-2, -3 and -9, and tissue inhibitor of metalloproteinases-1 in children with primary hypertension may indicate their role in the development of hypertension and/or on the presence of vascular remodelling at an early stage of the disease.

Keywords: matrix metalloproteinases, primary hypertension, children

Streszczenie

Wstęp: Nadciśnienie tętnicze pierwotne stanowi ważny problem zdrowotny u dzieci. Jego patogeneza jest wieloczynnikowa. Istotną rolę przypisuje się metaloproteinazom macierzy pozakomórkowej uczestniczącym w procesie przebudowy ścian naczyń, ale również wykazującym bezpośrednią aktywność wazokonstrykcyjną. **Cel:** Celem pracy było porównanie stężeń metaloproteinaz macierzy pozakomórkowej: 2, 3, 9 oraz tkankowego inhibitora metaloproteinaz macierzy pozakomórkowej 1 w surowicy dzieci z nadciśnieniem tętniczym pierwotnym i dzieci z ciśnieniem prawidłowym. **Materiał i metody:** W badaniu uczestniczyło 23 dzieci z nadciśnieniem pierwotnym w wieku 14,75 roku [mediana; rozstęp międzykwartylowy (*interquartile range*, IQR): 3,66] oraz 23 dzieci z prawidłowym ciśnieniem tętniczym w wieku 14,66 roku (mediana; IQR: 6,25). Stężenia osoczowych metaloproteinaz macierzy pozakomórkowej: 2, 3, 9 oraz tkankowego inhibitora metaloproteinaz macierzy pozakomórkowej 1 oznaczano metodą immunoenzymatyczną, wyniki porównywano za pomocą testu *U* Manna–Whitneya, przy poziomie istotności $p \leq 0,05$. **Wyniki:** W grupie dzieci z nadciśnieniem tętniczym pierwotnym stwierdzono istotnie wyższe stężenia osoczowych metaloproteinaz macierzy pozakomórkowej: 2 [178,1 (IQR: 35,84) *vs* 99,9 (IQR: 20,1) ng/ml], 3 [6,47 (IQR: 1,75) *vs* 2,67 (IQR: 1,08) ng/ml], 9 [191,1 (IQR: 52,75) *vs* 58,34 (IQR: 18,99) ng/ml] oraz tkankowego inhibitora metaloproteinaz macierzy pozakomórkowej 1 [863,9 (IQR: 192,9) *vs* 335,41 (IQR: 109,99) ng/ml] w porównaniu z dziećmi normotensyjnymi ($p < 0,00001$). Wartość wskaźnika metaloproteinaza macierzy pozakomórkowej 9/

tkankowy inhibitor metaloproteinaz macierzy pozakomórkowej 1 [0,22 (IQR: 0,1) *vs* 0,18 (IQR: 0,05)] była znamiennie wyższa w grupie dzieci z nadciśnieniem pierwotnym (p = 0,008). **Wnioski:** Podwyższone stężenia osoczowych metaloproteinaz macierzy pozakomórkowej: 2, 3, 9 oraz tkankowego inhibitora metaloproteinaz macierzy pozakomórkowej 1 u dzieci z pierwotnym nadciśnieniem tętniczym mogą wskazywać na ich udział w rozwoju nadciśnienia samoistnego i/lub na obecność zjawiska przebudowy naczyń już na wczesnym etapie choroby.

Słowa kluczowe: metaloproteinazy macierzy pozakomórkowej, pierwotne nadciśnienie tętnicze, dzieci

INTRODUCTION

Arterial hypertension (AH) is a pronounced health concern worldwide. AH carries a risk of cardiovascular disease and premature death due to the nature of its complications associated with vascular and cardiac remodelling, atherosclerosis, and target-organ failure[1,2]. AH affects more than 30% of adults and 3–5% of children, and its prevalence increases with age[3,4]. While in adults primary hypertension (PH) is the most common diagnosis, in children AH used to be attributed to underlying causes. Nowadays PH becomes dominant also in the paediatric population[5,6]. PH is described as a syndrome of interrelated neuro-immuno-metabolic abnormalities resulting in haemodynamic changes[7]. The pathogenesis of PH involves multiple systems leading to an increase in vasoactive hormonal factors, grow factors, reactive oxygen species, inflammation, and endothelial dysfunction[8]. The role of altered activity of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in the pathogenesis of PH has been proposed[9]. MMPs are a family of zinc-dependent endopeptidases produced by multiple cells and tissues including endothelial cells, vascular smooth muscle cells, fibroblasts, and immune cells[10]. MMPs act under the control of TIMPs, and they are engaged in extracellular matrix (ECM) remodelling, cell proliferation, differentiation, and migration[10,11]. Changes in the levels of MMPs and TIMPs are promoted by vasoconstrictive agents, which results in proteolysis of contractile proteins of ECM of the vascular wall and leads to vascular remodelling, but also sustains hypertension through the mechanism of "vicious cycle" and ultimately leads to the development of hypertension-mediated organ damage[11,12]. Among a large family of metalloproteinases, an essential role in remodelling processes has been attributed to MMP-2, MMP-3, and MMP-9[13,14]. Moreover, some experimental studies have implicated MMPs in the pathogenesis of PH through a direct impact of MMP-2 on the activity of vasoactive peptides or through MMP-mediated cleavage of beta2-adrenergic receptors in arterioles, contributing to arterial blood pressure elevation[15–18]. These observations may lead to the hypothesis that MMPs and their TIMPs play a role in the early stages of hypertension, which may be expected in children and adolescents with newly diagnosed PH. While in adults there are studies demonstrating increased circulating levels of MMP-2, MMP-3 and MMP-9, and either increased or decreased levels of TIMP-1 in hypertension, in children little information is available so far with respect to possible alterations in MMPs/TIMPs levels in PH[19–25]. Although one study showed elevated serum levels of MMP-9 in children with PH, and another indicated increased plasma concentrations of MMP-9, TIMP-1, and the MMP-9/TIMP-1 ratio in boys with PH, no previous work has investigated MMP-2 and MMP-3 serum concentrations in paediatric PH[24,25]. In the present study, we aimed at comparing the serum concentrations of MMP-2, MMP-3, MMP-9, TIMP-1 which inhibits MMP-9 as well as the MMP-9/TIMP-1 ratio as an indicator of MMP-9 net activity in children with newly diagnosed PH with those found in healthy, normotensive children.

MATERIALS AND METHODS

The study was performed according to the Declaration of Helsinki and with the approval of the Silesian Medical University Bioethical Committee. All the participants' parents, as well as the participants aged 16 years and older, provided their written informed consent. A total of 23 subjects, aged 14.75 years [median; interquartile range (IQR): 3.66] admitted to the Division of Paediatric Nephrology, Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland with newly diagnosed and untreated PH, who underwent a full diagnostic work-up to exclude secondary hypertension, were enrolled in the study. The control group consisted of 23 normotensive subjects aged 14.66 years (median; IQR: 6.25). The exclusion criteria comprised any chronic disease and/or chronic medication or any acute infection within one month preceding enrolment in the study, and incomplete data.

The blood pressure (BP) classification was based on office BP measurements according to the 2016 European Society of Hypertension guidelines and referred to the normative values developed for the Polish population of children aged 3–18 years[26,27]. Normal BP was defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP) <90th percentile for age, sex and height in children under 16 years, and BP <130/85 mm Hg in adolescents aged 16 years and over. Hypertension was defined in three separate BP measurements for SBP and/or DBP ≥95th percentile for age, sex, and height in children under 16 years, and SBP and/or DBP ≥140/90 mm Hg in adolescents aged 16 years and over. Grade 1 hypertension was defined for SBP and/or DBP 95th percentile to the 99th percentile and 5 mm Hg in children under 16 years and SBP and/or DBP 140–159/90–99 mm Hg in adolescents aged 16 years and over.

Grade 2 hypertension was defined for SBP and/or DBP >99th percentile plus 5 mm Hg in children under 16 years, and SBP and/or DBP 160–179/100–109 mm Hg in adolescents aged 16 years and over[26].

PH was diagnosed according to the Guidelines of the Paediatric Section of the Polish Society of Hypertension based on the *2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents* and was confirmed by 24-hour ambulatory blood pressure monitoring (ABPM) in line with the scientific statement from the American Heart Association and the 2016 European Society of Hypertension guidelines[26].

Screening for target organ damage with echocardiography to calculate the left ventricular mass index (LVMI) according to de Simone formula referred to percentile for age- and sex-based reference data, with the definition of left ventricular hypertrophy (LVH) for LVMI value above the 95th percentile and albuminuria above 30 mg/24 hours as an indicator of microvascular damage were the integral part of the diagnostic approach in the participants with PH according to the 2016 European Society of Hypertension guidelines[26].

The following parameters were evaluated in the study: age (years), height (cm), height (percentile) referred to the sex- and age-specific charts provided by OLAF (study on the population of Polish children aged 5–18 years), body mass index (BMI) (kg/m^2), BMI (percentile) referred to the sex- and age-specific charts provided by OLAF (study on the population of Polish children aged 5–18 years), estimated glomerular filtration rate (eGFR) calculated according to the Schwartz formula (mL/min/1.73 m^2), fasting glucose (mg/dL), total cholesterol (mmol/L), high-density lipoprotein – HDL-cholesterol (mmol/L), low-density lipoprotein – LDL-cholesterol (mmol/L), triglycerides (mmol/L), and uric acid (μmol/L)[27,28].

The blood samples for the measurement of serum concentrations of MMP-2, MMP-3, MMP-9, TIMP-1 were centrifuged, and serum specimens were stored at −70°C until the time of analysis. The serum concentrations of MMP-2, MMP-3, MMP-9, TIMP-1 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits BioVendor LLC (BioVendor – Laboratorní medicína a.s., The Czech Republic) according to the manufacturer's instructions. All intra-assay precision coefficients of variation were <5.3%. The lower limit of detection was 0.5 ng/mL, 0.1 ng/mL, 0.151 ng/mL, 0.1 ng/mL for MMP-2, MMP-3, MMP-9, TIMP-1, respectively. The serum concentration of MMP-9 was indexed to the serum concentration of its inhibitor TIMP-1 to assess the MMP-9/TIMP-1 ratio.

Statistical analysis

Database management and statistical analysis were performed with the data analysis software system STATISTICA (version 12, StatSoft, Inc.). The homogeneity of variance was checked with the Shapiro–Wilk test. The variables with a normal distribution were presented as mean and standard deviation values, whereas the variables with an abnormal distribution (MMP-2, MMP-3, MMP-9, TIMP-1 serum concentrations, MMP-9/TIMP-1 ratio, age of participants, height and BMI sex- and age-specific percentiles) were expressed as median and IQR values. The continuous variables with a normal distribution were compared with the Student *t*-test for independent variables. The continuous variables with an abnormal distribution were compared using the Mann–Whitney *U* test. The level of significance was set at $p \leq 0.05$.

RESULTS

The baseline and laboratory characteristics of the study samples (children with PH and children with normal BP) are summarised in Tab. 1 and 2. The participants with PH, with regard to the severity of hypertension, were mostly assessed as grade 1 hypertension (21 out of 23 children), with grade 2 hypertension diagnosed in only two children. None of the participants with PH presented with target organ damage (LVH and/or albuminuria >30 mg/24 hours). The study groups did not differ significantly in terms of age at the time of sampling. None of the study groups showed any signs of glomerular filtration impairment. The participants with PH were characterised by significantly higher height [172.31 ± 11.75 vs. 158.72 ± 19.00 cm], height percentile value [88 (IQR: 31) vs. 50 (IQR: 70) percentile], BMI value [27.6 ± 4.85 vs. 22.02 ± 4.50 kg/m^2] as well as BMI percentile value [98 (IQR: 15) vs. 72 (IQR: 40) percentile] than the normotensive controls ($p = 0.004$, $p = 0.015$, $p = 0.0006$, $p = 0.002$, respectively). There was a significant increase in serum uric acid levels [357.26 ± 68.95 vs. 278.04 ± 75.83 μmol/L] as well as in triglycerides levels [1.21 ± 0.57 vs. 0.87 ± 0.31 mmol/L] in the group with PH in comparison with the normal BP group ($p = 0.0003$, $p = 0.019$, respectively). The serum HDL-cholesterol concentrations were significantly lower in the PH group in comparison with the normotensive control group [1.22 ± 0.29 vs. 1.54 ± 0.38 mmol/L], $p = 0.002$. The serum concentrations of MMP-2, MMP-3, MMP-9, TIMP-1 and the calculated MMP-9/TIMP-1 ratios in the study groups are shown in Tab. 3. In the group with PH serum concentration of

Characteristic	*Primary hypertension* **N = 23**
Grade 1 hypertension	*n* = 21
Grade 2 hypertension	*n* = 2
LVH	*n* = 0
LVMI (g/m^{2,7})	33.06 ± 4.53
Albuminuria above 30 mg/24 hours	*n* = 0
Albuminuria (mg/24 hours)	10.48 ± 5.54
LVH – left ventricular hypertrophy; **LVMI** – left ventricular mass index.	

Tab. 1. Characteristics of participants with primary hypertension in terms of classification of hypertension based on office blood pressure measurements and evaluation of target organ damage

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Characteristic	Primary hypertension $N = 23$	Normal blood pressure $N = 23$	*p* value
Age [years]	14.75 (IQR: 3.66)	14.66 (IQR: 6.25)	NS
Height [cm]	172.31 ± 11.75	158.72 ± 19.00	0.004
Height [percentile]	88 (IQR: 31)	50 (IQR: 70)	0.015
BMI [kg/m^2]	27.6 ± 4.85	22.02 ± 4.50	0.0006
BMI [percentile]	98 (IQR: 15)	72 (IQR: 40)	0.002
eGFR [mL/min/1.73 cm^2]	98.97 ± 19.87	105.65 ± 19.85	NS
Uric acid [µmol/L]	357.26 ± 68.95	278.04 ± 75.83	0.0003
Glucose [mg/dL]	90.24 ± 6.40	90.28 ± 6.77	NS
Cholesterol [mmol/L]	3.87 ± 0.74	3.81 ± 0.68	NS
LDL-cholesterol [mmol/L]	2.10 ± 0.55	1.96 ± 0.44	NS
HDL-cholesterol [mmol/L]	1.22 ± 0.29	1.54 ± 0.38	0.002
Triglycerides [mmol/L]	1.21 ± 0.57	0.87 ± 0.31	0.019

BMI – body mass index; **eGFR** – estimated glomerular filtration rate; **HDL** – high-density lipoprotein; **IQR** – interquartile range; **LDL** – low-density lipoprotein; **NS** – non-significant.

Tab. 2. Baseline and laboratory characteristics of the study groups

Parameter	Primary hypertension $N = 23$	Normal blood pressure $N = 23$	*p* value
MMP-2 [ng/mL]	178.1 (IQR: 35.84)	99.9 (IQR: 20.1)	<0.00001
MMP-3 [ng/mL]	6.47 (IQR: 1.75)	2.67 (IQR: 1.08)	<0.00001
MMP-9 [ng/mL]	191.1 (IQR: 52.75)	58.34 (IQR: 18.99)	<0.00001
TIMP-1 [ng/mL]	863.9 (IQR: 192.9)	335.41 (IQR: 109.99)	<0.00001
MMP-9/TIMP-1 ratio	0.22 (IQR: 0.1)	0.18 (IQR: 0.05)	$p = 0.008$

IQR – interquartile range; **MMP-2** – matrix metalloproteinase-2; **MMP-3** – matrix metalloproteinase-3; **MMP-9** – matrix metalloproteinase-9; **TIMP-1** – tissue inhibitor of metalloproteinases-1.

Tab. 3. MMP-2, MMP-3, MMP-9, TIMP-1 serum concentrations and MMP-9/TIMP-1 ratio in the study groups

MMP-2 [178.1 (IQR: 35.84) vs. 99.9 (IQR: 20.1) ng/mL], MMP-3 [6.47 (IQR: 1.75) vs. 2.67 (IQR: 1.08) ng/mL], MMP-9 [191.1 (IQR: 52.75) vs. 58.34 (IQR: 18.99) ng/mL] and TIMP-1 [863.9 (IQR: 192.9) vs. 335.41 (IQR: 109.99) ng/mL] were significantly higher than in the group with normal BP, $p < 0.00001$ every parameter. The MMP-9/TIMP-1 ratio [0.22 (IQR: 0.1) vs. 0.18 (IQR: 0.05)] was also significantly elevated in the participants with PH when compared with the normotensive participants, $p = 0.008$.

DISCUSSION

This was a pilot study conducted in a group of children with newly diagnosed PH, focused on the assessment of serum concentrations of MMP-2, MMP-3, MMP-9 and TIMP-1, acting as MMP-9 inhibitor. Our work revealed significantly elevated levels of MMP-2, MMP-3, MMP-9, TIMP-1 and the MMP-9/TIMP-1 ratio in children with PH, which may indicate the vital importance of metalloproteinases and their inhibitors in the development of essential hypertension. PH is considered to be a process of early vascular ageing originating in childhood, driven by metabolic alterations and leading to growth acceleration and BP elevation, culminating in adulthood with functional and structural vascular remodelling[7]. The results of our study, carried out on a group of children with new-onset PH mostly classified with grade 1 hypertension with no symptoms of routinely screened target organ damage, seem to be corresponding with the theory outlined above. The participants with PH were characterised by significantly higher anthropometric parameters related to sex- and age-specific charts but also by metabolic disturbances in the form of higher serum concentrations of uric acid and triglycerides and lower serum concentration of HDL-cholesterol when compared to the normotensive peers. Significantly higher serum concentrations of MMPs and inhibitor TIMP-1 in children with PH may have reflected the activity of vascular remodelling present at the early stages of the disease, but they may have also revealed the role of MMPs as promotors of PH. Odenbach et al., in their experimental study, showed that angiotensin II had a potential to stimulate MMP-2 activation, which in turn led to an increase in the level of vasoconstrictive peptides[16]. Abdalvand et al. and Fernandez-Patron et al. proved that activated MMP-2 contributed to BP elevation by increasing the bioavailability of vasoconstrictors such as endothelin-1, and decreasing the bioavailability of vasodilators such as nitric oxide or calcitonin gene-related peptide[15,18]. In their article, Rodrigues et al. highlighted the phenomenon of MMP-mediated cleavage of the beta2-adrenergic receptors in arterioles, which enhanced arteriolar tone and contributed to BP elevation[17]. MMP-2 direct inhibition or MMP-2 indirect inhibition via

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angiotensin II receptor blockade prevented a rise in BP in animal models[16,29]. However, in the vast majority of experimental research, MMPs were described as key players in the processes of extracellular matrix modification, creation of proinflammatory environment, shift in the phenotypes of endothelial cells and vascular smooth muscle cells facilitating arterial remodelling, fibrosis, stiffening and BP increase[11–13]. The main role had been attributed to MMP-2, MMP-3 and MMP-9, metalloproteinases involved in the elastin network destruction and impairment of blood vessel elasticity but on the other hand metalloproteinases involved in collagen accumulation in hypertensive arterial walls as well as the processes of arterial calcification, maintenance of high BP, and the development of target organ damage[11,12,16,17]. In context with this evidence our investigation demonstrated significantly higher serum levels of MMP-2, MMP-3, MMP-9, TIMP-1 as well as the MMP-9/TIMP-1 ratio reflecting net activity of MMP-9 in children with untreated PH. The results of our study are in line with the findings obtained by Tayebjee et al. and Tan et al., reporting notably higher circulating plasma concentrations of MMP-9 and TIMP-1 in adult hypertensive patients[19,20]. On the other hand, Onal et al. described elevated serum levels of MMP-9 but lower concentrations of TIMP-1 in adult hypertensive participants prior to hypertensive treatment and MMP-9 decrease but TIMP-1 increase after starting antihypertensive therapy[21]. In the study by Niemirska et al., conducted in children with PH, elevated plasma concentrations of MMP-9, TIMP-1 and the MMP-9/TIMP-1 ratio were noticed in hypertensive boys[24]. Martinez-Aguayo et al. described elevated MMP-9 levels in children with PH[25]. Derosa et al. reported increased levels of MMP-2, MMP-9 and TIMP-1 in adult patients with hypertension[22]. The only published investigations focused on the plasma serum concentrations of MMP-2 in the paediatric population involved obese children and showed lower levels of MMP-2 in childhood obesity[30]. Our study showed elevated serum MMP-2 and MMP-3 levels in paediatric PH for the first time. According to the study by Rajzer et al., MMP-3 was increased in untreated hypertensive adults and correlated with hypertension-mediated arterial stiffening[14]. Wang et al., in their research on PH in adults, reported higher serum levels of MMP-3 in hypertensive participants; moreover, MMP-3 concentrations were significantly elevated in patients with PH and LVH when compared to patients with PH but no target organ damage[23]. The findings of our study, as well as the results of the above-mentioned studies, suggest that there might be a link between PH and increased MMPs activation, but further studies are needed to gain a deeper understanding of this potential relationship.

CONCLUSIONS

The results of our study show significantly increased serum concentrations of MMP-2, MMP-3, MMP-9, TIMP-1 and the MMP-9/TIMP-1 ratio in children with PH, which may indicate that metalloproteinases play a role in the development of PH, but may also suggest the presence of vascular remodelling at the early stage of the disease. Further research focused on the role of matrix metalloproteinases and their tissue inhibitors in the pathogenesis of PH in children and adolescents is expected.

Conflict of interest

The author does not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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References

1. Go AS, Mozaffarian D, Roger VL et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation 2014; 129: e28–e292.
2. Kannel WB: Hypertensive risk assessment: cardiovascular risk factors and hypertension. J Clin Hypertens (Greenwich) 2004; 6: 393–399.
3. Song P, Zhang Y, Yu J et al.: Global prevalence of hypertension in children: a systematic review and meta-analysis. JAMA Pediatr 2019; 173: 1154–1163.
4. Sharma AK, Metzger DL, Rodd CJ: Prevalence and severity of high blood pressure among children based on the 2017 American Academy of Pediatrics Guidelines. JAMA Pediatr 2018; 172: 557–565.
5. Gupta-Malhotra M, Banker A, Shete S et al.: Essential hypertension vs. secondary hypertension among children. Am J Hypertens 2015; 28: 73–80.
6. Flynn JT, Alderman MH: Characteristics of children with primary hypertension seen at a referral center. Pediatr Nephrol 2005; 20: 961–966.
7. Litwin M, Feber J, Niemirska A et al.: Primary hypertension is a disease of premature vascular aging associated with neuro-immuno-metabolic abnormalities. Pediatr Nephrol 2016; 31: 185–194.
8. Bautista LE: Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. J Hum Hypertens 2003; 17: 223–230.
9. Fontana V, Silva PS, Gerlach RF et al.: Circulating matrix metalloproteinases and their inhibitors in hypertension. Clin Chim Acta 2012; 413: 656–662.
10. Cui N, Hu M, Khalil RA: Biochemical and biological attributes of matrix metalloproteinases. Prog Mol Biol Transl Sci 2017; 147: 1–73.
11. Wang M, Jiang L, Monticone RE et al.: Proinflammation: the key to arterial aging. Trends Endocrinol Metab 2014; 25: 72–79.
12. Wang M, Zhang J, Telljohann R et al.: Chronic matrix metalloproteinase inhibition retards age-associated arterial proinflammation and increase in blood pressure. Hypertension 2012; 60: 459–466.
13. Basalyga DM, Simionescu DT, Xiong W et al.: Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases. Circulation 2004; 110: 3480–3487.

14. Rajzer M, Wojciechowska W, Kameczura T et al.: The effect of antihypertensive treatment on arterial stiffness and serum concentration of selected matrix metalloproteinases. Arch Med Sci 2017; 13: 760–770.

15. Abdalvand A, Morton JS, Bourque SL et al.: Matrix metalloproteinase enhances big-endothelin-1 constriction in mesenteric vessels of pregnant rats with reduced uterine blood flow. Hypertension 2013; 61: 488–493.

16. Odenbach J, Wang X, Cooper S et al.: MMP-2 mediates angiotensin II-induced hypertension under the transcriptional control of MMP-7 and TACE. Hypertension 2011; 57: 123–130.

17. Rodrigues SF, Tran ED, Fortes ZB et al.: Matrix metalloproteinases cleave the β_2-adrenergic receptor in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 2010; 299: H25–H35.

18. Fernandez-Patron C, Stewart KG, Zhang Y et al.: Vascular matrix metalloproteinase-2-dependent cleavage of calcitonin gene-related peptide promotes vasoconstriction. Circ Res 2000; 87: 670–676.

19. Tayebjee MH, Nadar S, Blann AD et al.: Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in hypertension and their relationship to cardiovascular risk and treatment: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). Am J Hypertens 2004; 17: 764–769.

20. Tan J, Hua Q, Xing X et al.: Impact of the metalloproteinase-9/tissue inhibitor of metalloproteinase-1 system on large arterial stiffness in patients with essential hypertension. Hypertens Res 2007; 30: 959–963.

21. Onal IK, Altun B, Onal ED et al.: Serum levels of MMP-9 and TIMP-1 in primary hypertension and effect of antihypertensive treatment. Eur J Intern Med 2009; 20: 369–372.

22. Derosa G, D'Angelo A, Ciccarelli L et al.: Matrix metalloproteinase-2, -9, and tissue inhibitor of metalloproteinase-1 in patients with hypertension. Endothelium 2006; 13: 227–231.

23. Wang X, Han W, Han L et al.: Levels of serum sST2, MMP-3, and Gal-3 in patients with essential hypertension and their correlation with left ventricular hypertrophy. Evid Based Complement Alternat Med 2021; 2021: 7262776.

24. Niemirska A, Litwin M, Trojanek J et al.: Altered matrix metalloproteinase 9 and tissue inhibitor of metalloproteinases 1 levels in children with primary hypertension. J Hypertens 2016; 34: 1815–1822.

25. Martinez-Aguayo A, Campino C, Baudrand R et al.: Cortisol/cortisone ratio and matrix metalloproteinase-9 activity are associated with pediatric primary hypertension. J Hypertens 2016; 34: 1808–1814.

26. Lurbe E, Agabiti-Rosei E, Cruickshank JK et al.: 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016; 34: 1887–1920.

27. Kułaga Z, Litwin M, Grajda A et al.; OLAF Study Group: Oscillometric blood pressure percentiles for Polish normal-weight school-aged children and adolescents. J Hypertens 2012; 30: 1942–1954.

28. Schwartz GJ, Muñoz A, Schneider MF et al.: New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009; 20: 629–637.

29. Nagareddy PR, Rajput PS, Vasudevan H et al.: Inhibition of matrix metalloproteinase-2 improves endothelial function and prevents hypertension in insulin-resistant rats. Br J Pharmacol 2012; 165: 705–715.

30. Glowińska-Olszewska B, Urban M, Florys B: [Selected matrix metalloproteinases (MMP-2, MMP-9) in obese children and adolescents]. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw 2006; 12: 179–183.

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