Review article

Primary Hypertension in Children and Adolescents: Risk Factors and Vascular Damage

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Abstract

The incidence of primary hypertension is on the rise in the pediatric population, with an approximate prevalence ranging from 3% to 5%. The most significant risk factors for the onset and development of primary hypertension are well-known, and some of them are preventable, including increased salt consumption and obesity. Connected with metabolic risk factors, elevated blood pressure in childhood is carried into adulthood. Primary hypertension is associated with attenuated vascular responses to various physiological stimuli in both peripheral microcirculation and systemic macrocirculation in adults and children. Endothelial dysfunction is one of the most important features of arterial hypertension, together with an increased level of oxidative stress – both determinants significantly contribute to all the pathophysiological changes observed in hypertension. Systemic arterial hypertension has emerged as a prevalent cardiovascular risk factor associated with substantial morbidity and mortality. Hence, the timely identification of individuals with elevated blood pressure and early-life blood pressure management could serve as a crucial strategy to mitigate the risk of cardiovascular disease and mortality in adulthood.

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Epidemiology, definition and classification of arterial hypertension in children and adolescents

Arterial hypertension is considered one of the most significant medical and public health problems in Western societies and the main, potentially reversible, cause of cardiovascular (CV) diseases. While juvenile arterial hypertension is less prevalent than in adults, the incidence of hypertension in children and adolescents has markedly risen in recent decades, partly attributed to the increasing prevalence of childhood obesity [1]. It should be pointed out that the rate of hypertension in children and adolescents is also determined by the definition used, which has changed over time and generally varies globally [2]. Approximately 3–5% of children and adolescents experience hypertension, while 10–14% exhibit elevated blood pressure (BP) levels, referred to as high normal BP [1, 3]. Therefore, hypertension represents one of the most common chronic diseases in adolescence [2]. Although it is multifactorially caused, among the most significant risk factors for hypertension are excessive salt intake and the epidemic of obesity among children. Given that primary hypertension already in childhood is often associated with subclinical target organ damage, it is not considered a simple hemodynamic problem, but the first stage in the development of cardiovascular diseases [4]. There is evidence indicating that hypertension in children may arise from a combination of genetic, environmental and biological factors. Children with elevated blood pressure have been observed to be at risk of developing hypertension in adulthood [5, 6], and evidence suggests that hypertension in adulthood has its origins in childhood [7].

The initial guidelines for blood pressure management in this age group were issued in 1977 [8]. Prior to that, there was no standardized definition of hypertension in the pediatric population, and blood pressure measurement was not routinely conducted in asymptomatic children and adolescents. While the association between blood pressure levels and cardiovascular disease is firmly established in adults, it is not clearly defined in children and adolescents. The development of cardiovascular complications in this age group is the outcome of the interplay between various risk factors and age. Consequently, the definition of reference values in the pediatric population is based on the percentile distribution of blood pressure values. According to the most recent guidelines from 2023 by the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH), it is advised to characterize hypertension based on percentile distribution [9]. In children, hypertension is defined as systolic and/or diastolic arterial pressure values equal to or exceeding the 95th percentile for age, sex and body height, as measured in three distinct assessments.

Table 1. Classification of arterial hypertension in the pediatric population refers to the 2023 ESH and ISH guidelines

	0–15 years SBP and/or DBP percentile	16 years and older SBP and/or DBP values (mmHg)
Normal	<90th	<130/85
High-normal	≥90th to <95th percentile	130-139/85-89
Hypertension	≥95th percentile	≥140/90
Stage 1 hypertension	95th percentile to the 99th percentile and 5 mmHg	140-159/90-99
Stage 2 hypertension	>99th percentile plus 5 mmHg	160-179/100-109

Values < 90th percentile are considered normal BP and values from 90th to 95th percentile are high normal pressure. Hypertension stage 1 is considered to be systolic and/or diastolic pressure values ≥ 95th to 99th percentile + 5 mmHg, and stage 2 > 99th percentile +5 mmHg. According to the same guidelines [9], hypertension in adolescents aged ≥ 16 years is classified as in adults; systolic and/or diastolic pressure values < 130/85 mmHg are considered normotension, values 130–139/85–90 mmHg are considered high normal pressure and values ≥ 140/90 mmHg hypertension (Table 1).

The most important modifiable risk factors for arterial hypertension in childhood

Excessive salt intake

Elevated salt consumption is widely acknowledged as a key contributor to increased BP and arterial hypertension [10, 11], with associations with various cardiovascular disease outcomes [12, 13]. Consequently, excessive salt intake is recognized as the primary preventable factor contributing to morbidity and mortality [14]. The link between excessive salt intake and elevated BP/arterial hypertension has been established in the pediatric population as well [3, 15, 16], and this is significant because essential hypertension during childhood is connected with the onset of arterial hypertension in adulthood [17].

According to the World Health Organization guidelines, the recommended daily intake of sodium for adults is 2 g/day (approximately 5 g of salt), whereas recommended values for children should be further reduced proportionally to energy requirements [18]. However, a large number of conducted studies indicate that in almost most countries of the world, the daily salt intake is significantly higher than recommended, ranging between 6 and 12 g of salt per day [19, 20]. The alarming results of the research conducted on the adult population in Croatia in 2008 (Croatian Action on Salt and Health (CRASH)) showed that the average daily salt intake in our population was 11.6 g, which is more than twice the recommended values of the World Health Organization [21]. Encouraged by this research, the Croatian Institute of Public Health and the Ministry of Health presented a strategic plan intending to reduce daily salt intake by 4% every year [22], and data from 2019 showed that the average daily salt intake in Croatia decreased by 1 .6 g of salt in the last 12 years [23].

Elevated salt intake is recognized as a firmly established risk factor for the onset of arterial hypertension, irrespective of body weight, gender and age. However, the precise etiopathogenetic mechanisms underlying the development of arterial hypertension and its connection to excessive salt consumption remain incompletely understood. A recent study by Bigazziet et al. [24] revealed that genetic polymorphisms, previously linked to salt-sensitive hypertension in adults, influence BP values and sodium excretion in the adolescent population. This suggests the potential for impairment in the physiological systems for sodium control from an early age. Traditionally, the primary association between sodium and arterial hypertension was believed to involve an elevation in extracellular volume due to the osmotic impact of sodium, particularly in salt-sensitive individuals. However, this mechanism came under scrutiny with the realization that sodium can be more efficiently stored in the body in a non-osmolar form [25]. Recent hypotheses suggest that salt could influence BP through varied and intricate mechanisms. An overabundance of salt intake might induce alterations in the physiological systems responsible for regulating the functions of the heart, circulatory system and/or kidneys. In individuals with hypertension, particularly those who are obese, there is increased activity in the sympathetic nervous system [26]. This autonomic alteration is evident even in pediatric populations, as higher sympathetic modulation and lower parasympathetic modulation have been observed in hypertensive children [27] and adolescents [28]. Sympathetic nervous system activation has dual effects: it enhances sodium reabsorption in the proximal tubule and stimulates the local renin-angiotensin-aldosterone system (RAAS). The latter, in turn, amplifies distal sodium reabsorption and sympathetic activity through angiotensin II.

Moreover, the development of sodium-sensitive arterial hypertension appears to be influenced by a combination of genetic, hormonal and neuroendocrine factors [29].

Suckling et al. proposed that the consumption of high-sodium food results in a temporary elevation of plasma sodium concentration, potentially exerting toxic effects on the vascular system [30]. The plasma sodium concentration can influence blood pressure by altering the "stiffness" of endothelial cells. Elevated "stiffness" in endothelial cells may reduce the activity of endothelial nitric oxide synthase (eNOS), increase vascular resistance and contribute to elevated blood pressure. This condition might subsequently prompt microvascular remodeling and a systemic proinflammatory state, leading to microvascular endothelial inflammation, anatomical remodeling and functional abnormalities [15].

Excessive salt consumption presents a significant public health challenge in the pediatric population, with numerous studies establishing a link between high salt intake and elevated BP values [31, 32]. Recent meta-analyses have demonstrated an association between sodium intake and BP levels in children and adolescents. A compilation of eighteen studies examining sodium intake and BP demonstrated that each additional gram of daily sodium intake was correlated with a rise of 0.8 mmHg in systolic BP and 0.7 mmHg in diastolic BP. This association was more pronounced among overweight children and children with low potassium intake [16]. Supporting the notion that high salt intake contributes to elevated BP in children, a meta-analysis conducted a few years ago, encompassing 10 studies in children and adolescents, showed that reducing salt intake resulted in a decrease in BP (1.17 mmHg reduction in systolic BP and 1.29 mmHg reduction in diastolic BP). This provides robust evidence for the importance of limiting dietary salt intake in the early years of life [33]. In our previous study, we demonstrated that the estimated daily salt intake was 7.09 [5.25–9.59] g/day for children with normal BP and 10.7 [4.0–14.7] g/day for children with essential arterial hypertension. These findings underscore that, overall, children are consuming significantly more salt than the recommended values, particularly those with hypertension. Additionally, we validated the relationship between daily salt consumption, BP and body weight in the pediatric population [34]. Given the continuity of BP from childhood to adulthood, these findings suggest that reducing sodium intake during childhood and adolescence may contribute to lower BP and help prevent the development of hypertension later in life.

Overweight children and obesity

Another important modifiable factor that significantly affects the BP value at the individual and population level is obesity. In recent decades, in addition to the increase in arterial hypertension, there has also been a significant increase in the frequency of obesity in children and adolescents, and it is becoming one of the leading public health and medical problems. An alarming number of overweight and obese children has been recorded in all European countries, and it is estimated that more than 340 million children and adolescents aged 5 to 19 years are overweight or obese [35]. It is predicted that by 2025 there will be two billion overweight and obese people in the world. Unfortunately, Croatia also follows global negative trends and ranks high in fifth place with other countries in the Mediterranean region of Europe [36]. Our national study EHUH (Epidemiology of Hypertension in Croatia) showed that almost 70% of individuals whose body mass index (BMI) is greater than 30 kg/m2 also have arterial hypertension [37], while the studies conducted on children from second and third grade of elementary school showed that obesity is the main risk factor for the development of arterial hypertension already at that age. The results of the European initiative to monitor obesity in children (2018–2022) show a worrying proportion of children with excess body weight and obesity. Overall, almost every third child in the European region (29%) is overweight and obese, and in Croatia, 34.9% of children are overweight or obese [38].

According to the guidelines of the Pediatric Endocrinology Society [39], standardized BMI centile curves are used to assess the obesity degree in children and adolescents older than two years. BMI is obtained by dividing body mass in kilograms by the square of height in meters. Individual is considered overweight with BMI > 85th centile, and obese with BMI > 95th centile for age and sex according to revised centile curves [40].

Numerous studies indicate the connection between obesity and hypertension in children and emphasize the increased prevalence of hypertension in children with excessive body weight, indicating obesity is one of the main risk factors for the development of arterial hypertension in children [1]. In addition to arterial hypertension, childhood obesity is associated with an increased risk of developing numerous other health problems such as dyslipidemia, type 2 diabetes and left ventricular hypertrophy, all of which increase the risk of CV disease in adulthood [41]. The above is proof of the necessity of prevention and treatment of obesity in children.

Obesity in children is the result of a complex interaction of genetic, environmental, behavioral and socioeconomic factors [42], and unhealthy diet, lack of physical activity and insufficient sleep are increasingly present risk factors. Early recognition of obesity and the application of prevention measures are key to combating this problem. These include promoting a balanced diet, regular physical activity, reduction of sedentary lifestyle and education about healthy lifestyles. It is important to point out that the fight against childhood obesity requires a comprehensive approach at the global, national and individual level in order to create an environment that encourages healthy lifestyle habits [43].

Numerous potential pathophysiological pathways elucidate the link between obesity and increased BP as well as hypertension. Central to these pathways is the principle tied to dysfunctional adipocytes and the neurohormonal activation of the sympathetic nervous system. It is crucial to highlight that adipocytes function not solely as fat storage units but also as active endocrinological organs. The presence of excessive body weight and obesity is characterized by an augmented mass of adipose tissue, encompassing adipocytes, macrophages, fibroblasts and other cells [44]. Adipose tissue releases a variety of hormones and cytokines, referred to as adipokines, with increased secretion in the state of obesity. An imbalance arises when pro-inflammatory adipokines (such as leptin and resistin) predominate over anti-inflammatory adipokines (like adiponectin), resulting in dysfunctional adipose tissue and a persistent inflammatory condition. Several of these adipokines contribute to increased activity in the sympathetic nervous system, and research on humans has demonstrated that a leptin deficiency is linked to reduced sympathetic nervous system activity [45].

Activation of the sympathetic nervous system can impact various organs, with a noticeable preference for affecting the renal vasculature in cases of obesity. An elevation in BMI correlates with an increased secretion of noradrenaline [46]. In addition to its direct vasoconstrictive effects, increased sympathetic nervous system activity contributes to elevated BP and hypertension by enhancing the activity of the renin-angiotensin-aldosterone system. RAAS activity directly raises BP through angiotensin II-mediated vasoconstriction and indirectly through angiotensin II- and aldosterone-mediated salt and water reabsorption. As adipose tissue increases, RAAS activity intensifies, given that adipocytes also release RAAS hormones and mineralocorticoid stimulating factors [47]. Furthermore, obesity is linked to inflammation, as evidenced by macrophage infiltration in adipose tissue, and an elevated level of free fatty acids. Dyslipidemia, often present in obesity, is characterized by elevated LDL-cholesterol and triglycerides and low HDL-cholesterol. Elevated cholesterol is a known complex risk factor for CV diseases, contributing to increased BP and hypertension. Apart from inducing atherosclerosis, elevated LDL-cholesterol prompts chronic inflammation, activates the sympathetic nervous system and

enhances the activity of the RAAS system. [84]. Finally, obesity leads to complete metabolic dysfunction, which leads to impaired endothelial and vascular function and hypertension as a clinically recognizable outcome [48].

Hypertension, oxidative stress and vascular (dys)function

Primary hypertension in children is not harmless and can cause significant target organ damage, which is sometimes registered already at the time of diagnosis. Although CV disease is very rare in childhood, target organ damage represents a significant risk for developing CV events in adulthood. Over the past two decades, non-invasive markers have emerged and been employed to rate the progression of atherosclerosis and vascular dysfunction in the pediatric population. The non-invasive assessment of vascular structures and functions, utilizing tools like ultrasound and laser Doppler devices, has the potential to enhance screening programs for primary prevention in childhood. Additionally, incorporating vascular biomarkers as surrogates for CV risk in childhood could further improve these efforts [49].

Elevated BP in childhood and adolescence was found to be associated with increased carotid intima-media thickness, increased left ventricular mass and arterial stiffness [50]. Using laser Doppler flowmetry it has been shown that skin microvascular reactivity was significantly reduced in hypertensive subjects compared to normotensive controls [51]. Endothelial dysfunction plays a prominent role in the development of atherosclerosis and hypertension, and impaired endothelium reactivity is considered an initial sign of functional atherosclerotic changes [52–54]. When hypertension is present, the diminished availability of nitric oxide (NO) is partially offset by the activation of alternative pathways. This includes the production and release of endothelium-derived hyperpolarizing factor (EDHF), which plays a role in sustaining endothelium-dependent vasodilation [55]. Additionally, the intricate interplay between NO and endothelin (ET-1) may play a role in the progression of endothelial dysfunction in hypertension. Even with normal circulating levels of ET-1, individuals with hypertension exhibit increased vasoconstrictor activity of the peptide in the peripheral circulation, accompanied by a decrease in NO availability [56]. At the vascular level, by binding to its specific receptors mainly localized in smooth muscle cells, ET-1 stimulates vascular contraction and hypertrophy [57]. In addition to smooth muscle cells, ET-1 also binds to a large number of its receptors on endothelial cells and mediates the release of NO, thereby inhibiting vasoconstriction and cell proliferation. When endothelial dysfunction is evident, the activation of receptors on endothelial cells fails to enhance vasodilation mediated by NO, and the vasoconstrictive impact of ET-1 is increased [57]. This occurrence is further triggered by the diminished inhibitory influence of NO on the production and activity of ET-1 [55]. The overall disturbed equilibrium between these two systems can result in increased vasoconstrictive and proliferative activity of endothelin-1.

The most commonly used non-invasive technique for endothelial dysfunction detection in conduit arteries is flow-mediated dilation (FMD). A reduced FMD holds the potential to anticipate and detect risk factors for cardiovascular events, even in individuals without apparent symptoms [53]. In addition to the attenuated microvascular reactivity, arterial hypertension is also associated with reduced endothelium-dependent function of conduit artery circulation [58]. Brachial artery FMD was significantly weakened in children and adolescents with CV risk factors, including hypertension [59]. Because the number of studies on childhood microvascular and macrovascular function in primary hypertension is limited, the exact mechanisms of endothelial dysfunction are still not fully understood. However, what is well known is the early onset of atherosclerosis already in childhood, which is influenced by numerous risk factors, among them hypertension [60], suggesting that finding a reliable diagnostic tool for assessing early vascular changes is of great importance for

understanding the pathophysiological development of the disease.

Furthermore, since the increased level of oxidative stress is an important event in the development of vascular function disorders, it is necessary to evaluate its role in this function. A growing body of evidence suggests that oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and nitric oxide, plays a pivotal role in the development of hypertension [61]. Excessive production of harmful ROS, surpassing the cellular antioxidant capacity, results in pathogenic oxidative stress [62]. In clinical settings, markers of systemic inflammation and oxidative stress are employed to establish a connection between vascular damage and endothelial dysfunction. While limited clinical studies have explored the role of oxidative stress in children with primary hypertension, the findings from these studies indicate a strong association between oxidative stress and primary hypertension, irrespective of BMI. Moreover, this association correlates with the severity of hypertension, target organ damage and other metabolic and immunologic abnormalities. In their study, Warolin and colleagues have found an elevated iso-prostane urinary excretion in obese children and adolescents, that is connected with visceral obesity regardless of BMI and BP [63]. Furthermore, a study in which normotensive and hypertensive age-matched and sex-matched children were compared demonstrated that hypertensive children had significantly increased levels of symmetrical and asymmetrical dimethylarginine in serum [64]. Turi et al. demonstrated significant alterations in oxidative stress biomarkers associated with the severity of hypertension in hypertensive children, such as glutathione depletion in red cells, when compared to age- and BMI-matched normotensive controls [65]. The correlation between the level of oxidative stress and higher blood pressure values was also observed in prepubertal children [66]. Studies on untreated primary hypertension in children revealed disrupted markers of oxidative stress, including increased thiobarbituric acid reactive substances, decreased glutathione and increased glutathione peroxidase activity [67].

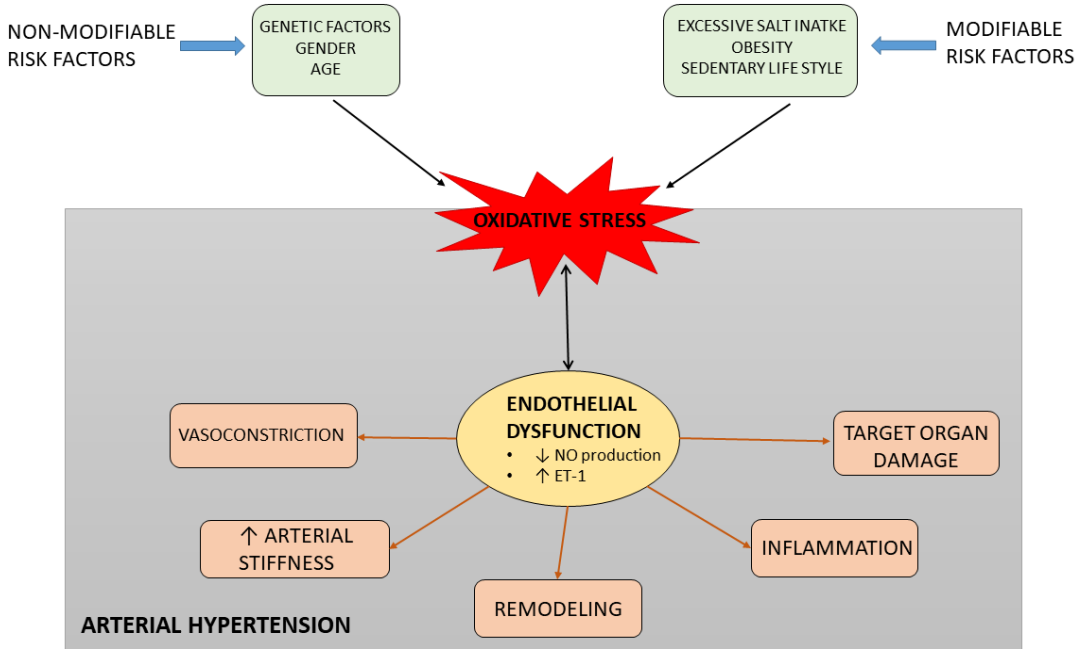

Figure 1. Risk factors for the development of endothelial dysfunction and arterial hypertension

Furthermore, serum thiobarbituric acid reactive substances were linked with left ventricular hypertrophy and concentric remodeling. Additionally, various oxidative stress biomarkers showed correlations with inflammatory activity, albumin excretion and systolic BP [67]. Despite abundant evidence supporting the role of oxidative stress in hypertension development and the potential preventive measures of antioxidant therapy, unresolved aspects regarding clinical translation remain.

Conclusion

Hypertension in children and adolescents has a significant impact on the quality of life in adulthood due to the increased cardiovascular risk since arterial hypertension is one of the main risk factors for the development of morbidity and mortality in the world. It has become a public health problem due to the increase in the prevalence of hypertension, primarily due to the childhood obesity epidemic. Arterial hypertension is associated with impaired NO balance, increased oxidative stress and vascular endothelial dysfunction, which further leads to various organ damage (Figure 1). Therefore, early prevention already in childhood – reducing salt intake and a balanced and healthy diet, as well as appropriate physical activity is of utmost importance for reducing the overall cardiovascular risk

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Competing interests. None to declare.

List of abbreviations:

BMI – body mass index
BP – blood pressure
CRASH – Croatian Action on Salt and Health
CV – cardiovascular
EHUH – Epidemiology of Hypertension in Croatia
eNOS – endothelial nitric oxide synthase
ESH – European Society of Hypertension
EDHF – endothelium-derived hyperpolarizing factor
ET-1 – endothelin 1
FMD – flow-mediated dilation
ISH – International Society of Hypertension
NO – nitric oxide
RAAS – local renin-angiotensin-aldosterone system
ROS – reactive oxygen species

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Primarna hipertenzija u djece i adolescenata: čimbenici rizika i vaskularno oštećenje

Učestalost primarne hipertenzije u porastu je u pedijatrijskoj populaciji, s približnom prevalencijom od 3 do 5 %. Najznačajniji čimbenici rizika za nastanak i razvoj primarne hipertenzije dobro su poznati, a neke je od njih moguće spriječiti, uključujući povećanu konzumaciju soli i pretilost. Povezano s metaboličkim čimbenicima rizika, povišen krvni tlak u djetinjstvu prenosi se u odraslu dob. Primarna hipertenzija povezana je s oslabljenim vaskularnim odgovorima na različite fiziološke podražaje u perifernoj mikrocirkulaciji i sistemskoj makrocirkulaciji kod odraslih i djece. Disfunkcija endotela jedna je od najvažnijih značajki arterijske hipertenzije, zajedno s povećanom razinom oksidativnog stresa - oba čimbenika značajno doprinose svim patofiziološkim promjenama koje se opažaju kod hipertenzije. Sistemska arterijska hipertenzija postala je raširen kardiovaskularni čimbenik rizika povezan sa značajnim morbiditetom i smrtnošću. Stoga bi pravovremena identifikacija osoba s povišenim krvnim tlakom i upravljanje krvnim tlakom u ranom životu moglo poslužiti kao ključna strategija za smanjenje rizika od kardiovaskularnih bolesti i smrtnosti u odrasloj dobi.