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EDUCATIONAL REVIEW

The changing face of pediatric hypertension in the era of the childhood obesity epidemic

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Abstract Historically, hypertension in childhood was thought to be an uncommon diagnosis, usually related to an underlying condition, most often parenchymal renal disease. Primary hypertension in childhood was felt to be quite rare. However, the worldwide childhood obesity epidemic has had a profound impact on the frequency of hypertension and other obesity-related conditions with the result that primary hypertension should now be viewed as one of the most common health conditions in the young. This review will present updated data on the prevalence of hypertension in children and adolescents, the impact of the childhood obesity epidemic on hypertension prevalence and blood pressure levels, shifts in how often primary hypertension is being diagnosed in childhood, and an overview of the pathophysiology of obesity-related hypertension. It is hoped that improved understanding of the significance of these issues will lead to improved recognition and treatment, which will be the key to averting an epidemic of cardiovascular disease in adulthood.

Keywords Obesity · Hypertension · Children · Adolescents · Epidemiology

Introduction

There is a worldwide epidemic of childhood obesity, which shows no signs of abating. In the United States, where the problem of childhood obesity has received considerable attention, up to 18 % of children and adolescents are classified as obese (defined as Body Mass Index [BMI] ≥95th percentile for age and gender) [1]. Combined prevalence of overweight and obesity of between 20 and 30 % have been recently reported in various European countries, including, Spain, Italy, and Greece [2–4]. Similar findings are being seen in non-Western countries as well. A recent meta-analysis in India of studies performed over the last decade found the prevalence rate of overweight (BMI ≥85th and <95th percentile) to be over 12 % and that of obesity to be over 3 % [5]. Among Indian children from higher socioeconomic classes, the rates are even higher, with overweight rates of 16–19 % and obesity rates of 5–6 % [6]. Higher socioeconomic status is associated with obesity in several developing African countries, in contrast to developed nations, where higher socioeconomic status appears to be protective [7]. Similarly, a quickly increasing rate of overweight and obesity among children has been found in other countries, including Thailand, China, Brazil, and South Africa [8, 9]. Worldwide, the overall prevalence of overweight and obesity in children increased by about 2.5 percentage points between 1990 and 2010. That year, the estimated prevalence among the world's children was 6.7 %. At the current rate of increase, it is expected to exceed 9 % by 2020 [10].

In addition to the alarming rate of rise in childhood overweight and obesity, the rates of obesity-related comorbidities such as type 2 diabetes mellitus and the metabolic syndrome are also increasing [11]. A recent analysis of data from National Health and Nutrition Examination Survey (NHANES) surveys conducted in the United States between 1999 and 2008 showed that 14 % of adolescents aged 12–19 years had prehypertension or hypertension, 22 % borderline-elevated or elevated low-density lipoprotein cholesterol, 6 % decreased high-density lipoprotein cholesterol (<35 mg/dL), and 15 % impaired glucose tolerance or diabetes during the survey period [12]. Overweight and obese Greek children also demonstrated higher BP, lower high-density lipoprotein cholesterol (HDL-C), and higher triglycerides compared with normal-weight children

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[4]. Given these data, the potential impact of the childhood obesity epidemic cannot be underestimated.

Frequency of childhood hypertension

Hypertension in children is defined as a systolic or diastolic blood pressure (BP) value ≥95th percentile for age, gender and height according to normative data derived from analysis of a large database of BP readings obtained in healthy children [13]. Thus, by definition, one might think that around 5 % of children and adolescents will have "elevated BP". BP screening studies conducted over the years, however, have demonstrated that this is not the case. Table 1 summarizes a number of BP screening studies conducted between 1974 and 2012 [14–23], and demonstrates that with repeated measurements, the actual prevalence of hypertension has generally been about 2–3.5 %, although a few recent studies seem to show an increase toward 4–5 %, at least among certain sub-groups of children. As will be discussed later, much of the rise in prevalence of childhood hypertension appears to be fueled by the obesity epidemic.

Some of the most reliable recent data on the frequency of hypertension in children come from the Houston BP screening project [20, 21], in which the investigators obtained repeated BP measurements from children and adolescents in public schools. Following Fourth Report recommendations to obtain repeated BP measurements in children with initial BP values >95th percentile, they demonstrated a prevalence of hypertension of 3.2 % after three screenings [21]. Of interest is that nearly 20 % of children had an initially elevated BP at the first screening—9.5 % were in the pre-hypertensive range, and 9.4 % in the hypertensive range—emphasizing the importance of repeated measurements in establishing the true prevalence of hypertension.

A national perspective on changes in hypertension prevalence in the United States can be found in a review of BP data in 8- to 17-year-old children from the NHANES and other related population-based studies conducted between 1963 and 2002, which clearly demonstrated an increase in the prevalence of high BP in children [26], countering earlier suggestions that the prevalence of childhood hypertension has remained stable over time [27]. The most recent survey data indicate that the prevalence of pre-hypertension has now reached 10 %, and the prevalence of hypertension nearly 4 %. A significant strength of this analysis was the application of current BP criteria for hypertension and pre-hypertension in childhood to all of the data in the various surveys included, thereby eliminating one of the problems affecting prior analyses [28]. Of note, this study also demonstrated that the recent trends in high BP have had a much greater effect on non-Hispanic blacks and Mexican–Americans than on whites [26]; illustrating that the increased cardiovascular risk seen in ethnic minorities in the US likely begins at a young age.

Screening studies conducted outside of the United States have demonstrated similar findings. Investigators in Brazil found that among 611 students aged 7 to 14 years, 16.6 % had elevated BP at the first screening and that 2.5 % had confirmed hypertension after three screenings [29]. In Reykjavik, Iceland, the prevalence of elevated BP in 9- and 10-year-old children was 13.1 %, 6.0 %, and 3.1 %

Table 1 Prevalence of hypertension in children and adolescents from screening studies

Study location	Number screened	Age (years)	Number of screenings	Normative criteria	Prevalence	Reference
Edmonton, Canada	15,594	15–20	1	150/95	2.2 %	Silverberg et al. [14]
New York, United States	3,537	14–19	2	140/90	1.2 % SHTN 2.4 % DHTN	Kilcoyne et al. [15]
Dallas, United States	10,641	14	3	95th percentile	1.2 % SHTN 0.4 % DHTN	Fixler et al. [16]
Minneapolis, United States	14,686	10–15	1	1987 TF	4.2 %	Sinaiko et al. [17]
Tulsa, United States	5,537	14–19	1	1987 TF	6.0 %	O'Quin et al. [18]
Minneapolis, United States	14,686	10–15	2	1996 WG	0.8 % SHTN 0.4 % DHTN	Adrogue et al. [19]
Houston, United States	5,102	12–16	3	1996 WG	4.5 %	Sorof et al. [20]
Houston, United States	6,790	11–17	3	4th Report	3.2 % HTN 15.7 % PHTN	McNiece et al. [21]
Reykjavík, Iceland	1,071	9–10	3	4th Report	3.1 %	Steinthorsdottir et al. [22]
Changsha, China	88,974	12–17	3	4th Report	3.1 % HTN 7.2 % PHTN	Cao et al. [23]

DHTN diastolic hypertension, *PHTN* pre-hypertension, *SHTN* systolic hypertension, *TF* Second Task Force Report [24], *WG* Working Group Report [25], *4th Report* The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [13]

after the first, second, and third screenings respectively [22]. And in India, a study of ~1,200 adolescents aged 11–17 years identified hypertension in 5.9 % and pre-hypertension 12.3 % after two screenings [30].

From the studies summarized here, we can see that childhood hypertension appears to have an overall prevalence of 2.5–3 %, and pre-hypertension a prevalence of 9–12 % when repeated screenings are performed. Recent studies demonstrate that prevalence is generally similar in different countries. This makes elevated BP one of the most common health conditions in childhood.

Impact of obesity on childhood blood pressure

Many studies over the years have indicated both that hypertension occurs more commonly among obese children than non-obese children, and that obesity itself increases BP. Illustrating the first point is a study conducted in Anadarko, Oklahoma [31]. 762 schoolchildren (grades kindergarten through 12—ages 5 through 18) were screened for height, weight, and BP. 62.4 % were Native American, 27.3 % were white, 6.0 % were African–American, and 4.3 % were Hispanic. 27.9 % of the students were obese (BMI >95th percentile), and the prevalence of obesity was greatest among Native Americans (32.2 %). 18 % had BP >90th percentile on the first screening and 2.8 % had persistently elevated BP after three screenings. BMI ≥85th percentile was associated with an increased relative risk of persistent BP elevation compared with normal-weight children [31].

Similarly, in the initial school screening study from Houston mentioned previously [20], the prevalence of hypertension was as high as 11 % among children whose BMI was ≥95th percentile, compared with a prevalence of 2–3 % among those with a normal BMI (75th percentile or lower). In a cross-sectional study conducted in Indiana, the risk of hypertension increased four-fold once BMI increased above the 85th percentile [32]. That study also showed that the negative effect of increased BMI on BP could be seen even in mildly overweight children. Most recently, in a study of Chinese adolescents 12–17 years of age [23], being overweight or obese markedly increased the risk of having both hypertension and pre-hypertension. Among Chinese adolescent boys, approximately 20 % of those with BMI at or above the 95th percentile had hypertension, and approximately 18 % had pre-hypertension. Rates were lower in girls, about 12 % for hypertension and 21 % for pre-hypertension. For both boys and girls in that study with normal BMI, rates were generally below 5 % [23].

The effect of obesity on absolute BP levels was clearly demonstrated by Luepker and colleagues in a study of secular trends in childhood BMI and BP [33]. They obtained anthropometric measurements and BP readings in 18,000 Minneapolis school children in 1986 (8,000 children) and 1996 (10,000 children). Over that time period, they found that the BMI of boys had increased from 19.7 to 20.5 kg/m^2, and that of girls had increased from 20.3 to 21.2 kg/m^2. Mean systolic BP had increased from 106.3 to 107.8 mmHg for boys and from 105.6 to 106.3 mmHg for girls, while mean diastolic BP had decreased. They also found that the association of weight and systolic BP was 2.5 times greater than that for height and systolic BP [33]. Thus, an increase in childhood BMI over time was accompanied by an increase in systolic BP. More recently, Simonetti et al. [34] demonstrated that BMI was strongly associated with BP levels in pre-school children, indicating that this effect begins at an early age.

A similar effect of obesity on BP levels was found in a 2004 examination of NHANES data [35]. Investigators compared BP data from NHANES surveys conducted in 1999–2000 with NHANES III, which was conducted from 1988 to 1994. They found an increase in BP levels of 1.4 mmHg for systolic BP and 3.3 mmHg for diastolic BP; increases were greater in 8- to 12-year-olds than in 13- to 17-year-olds, and were also greater in black and Mexican–American children than in white children [35]. Further analysis demonstrated that the increase in childhood overweight explained much of the increase in BP levels.

Taken together, these cross-sectional studies clearly suggest a significant impact of obesity on the prevalence of childhood hypertension, and even on absolute BP levels. The larger studies that have examined populations of children at different time points are perhaps most worrisome, as even small increases in BP are known to significantly increase the risks of cardiovascular disease and hypertensive kidney disease over the long term.

Impact of obesity on the etiology of childhood hypertension

The increase in frequency of primary hypertension in childhood can be seen by an examination of data from referral series of hypertensive children (Fig. 1). In the 1980s, Feld and Springate [36] reviewed published data on the etiology of hypertension in children at both primary and tertiary care centers. At tertiary centers, primary hypertension represented just 16 % of cases, with renal parenchymal diseases representing 70 % of those with secondary hypertension. Obesity-related hypertension was not mentioned as being seen at tertiary care centers; whether this was because such children were classified differently was not stated. Of note, they did report that 45 % of hypertensive children seen at primary care centers had obesity-related hypertension, with another 27 % had essential hypertension. Accordingly, secondary hypertension only accounted for 28 % of cases at

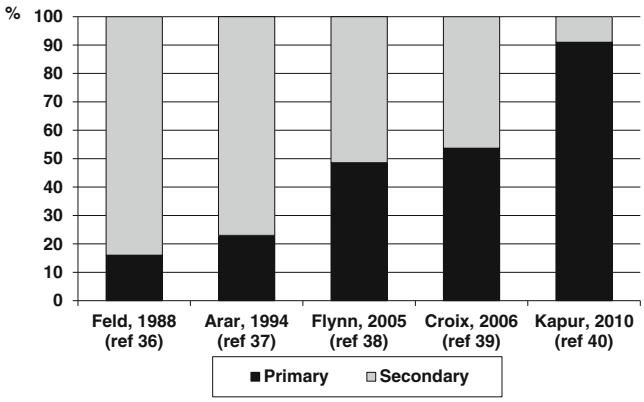

Fig. 1 Frequency of primary hypertension in pediatric referral series

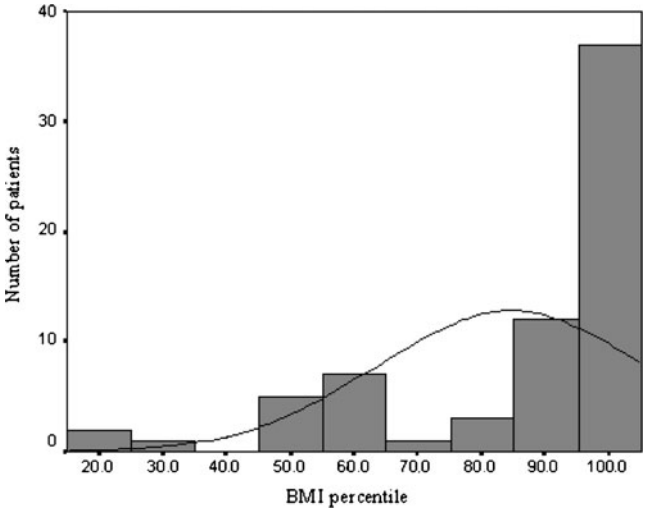

Fig. 2 Distribution of body mass index (BMI) percentiles among 70 children with primary hypertension

primary care centers. Feld and Springate go on to elucidate problems with the diagnosis of obesity-related hypertension, and recommend categorizing it as a form of secondary hypertension, which they admit was a controversial view at the time.

The inclination to automatically categorize most hypertension in children as having secondary causes can also be seen in a series published by Arar in the early 1990s [37]. In their experience, only 23 % of children evaluated for sustained hypertension had primary hypertension; most of these were adolescents aged 12–18 years. They recommended that for most hypertensive children, a thorough evaluation for secondary causes should be performed, particularly in younger children.

Subsequent publications, however, have demonstrated that even at referral centers, a greater proportion of hypertensive children are being diagnosed with primary hypertension. In a series from the University of Michigan summarizing the evaluation of 159 children seen over 5 years, 48.3 % of patients were found to have primary hypertension [38]. The impact of obesity on the diagnosis of primary hypertension in that series can be seen in Fig. 2, which illustrates the distribution of BMI percentiles of those children with primary hypertension. As can be seen, there is a marked shift in the distribution, with about two thirds of patients at a BMI percentile of 90 % or higher. Similarly, in a series of 259 hypertensive children seen at a Texas Children's Hospital [39], approximately 54 % had primary hypertension. In that series, children with primary hypertension were significantly older than those with secondary hypertension (14.5±2.4 year vs 10.6± 5.4 year, P=0.02), and also proportionately heavier than those with secondary hypertension (mean BMI percentile 88±14 vs 68±33 kg/m^2, P=0.012). This latter finding again highlights the impact of obesity of childhood hypertension in the current era.

With the exception of the study by Feld and Springate [36], all of the above data come from single-center referral series. However, recent data from multicenter studies have had similar results. In a study from four centers of the Midwest Pediatric Nephrology Consortium in the United States [40], 91 % of children who were evaluated for persistent hypertension had no underlying cause identified. Additionally, 89 % of those with primary hypertension had a BMI >85th percentile, and the mean BMI of those with primary hypertension was 35.9 kg/m^2, which was substantially higher than the mean BMI of those with secondary hypertension (25.4 kg/m^2). Similarly, in a recent description of the characteristics of 351 participants in two pediatric hypertension drug trials, secondary hypertension predominated only among children less than 6 years of age [41]. Finally, in an analysis of 2,900 children being treated with antihypertensive medications in the United States, primary hypertension was nine times more common than secondary hypertension [42]. While these latter studies have important limitations, they do reinforce the suggestion from single-center studies that primary hypertension should be considered the most likely diagnosis in a hypertensive child, and that this is especially true among those 6 years of age and older.

Mechanisms of hypertension in obesity

The pathophysiology of obesity hypertension is complex (Fig. 3) and has been reviewed in detail elsewhere [43–45]. A few major mechanisms are worth highlighting. Insulin resistance and hyperinsulinemia, both of which are present in obesity, are independent activators of the renal sympathetic nervous system (SNS). This, in turn, causes vasoconstriction and reduced renal blood flow, which is a trigger for renin release. The end result of this activation of

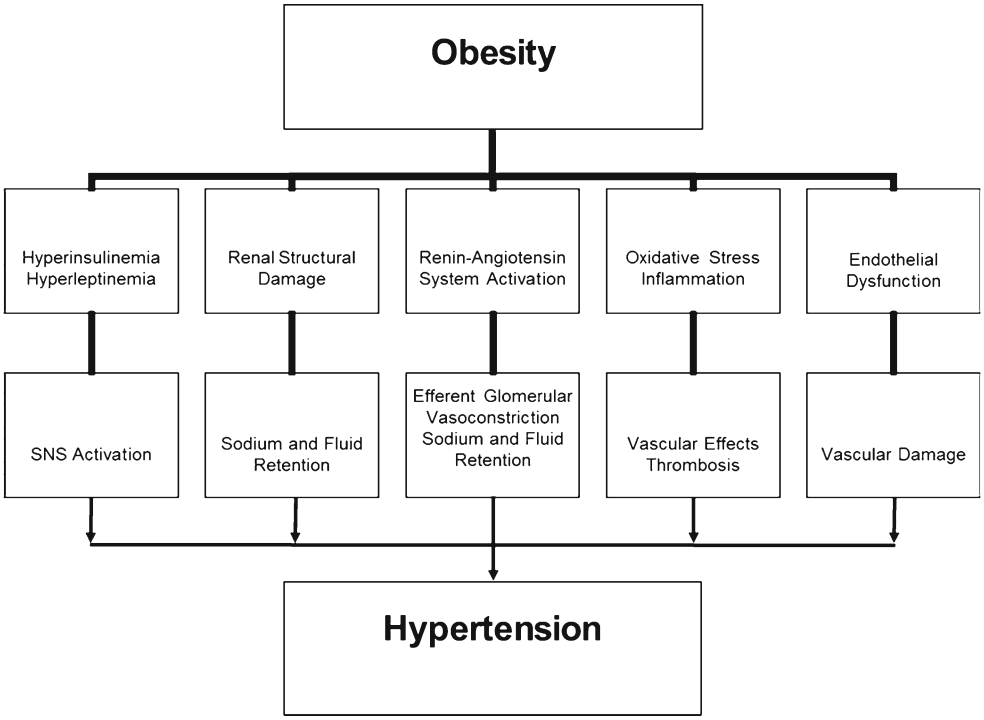

Fig. 3 Potential mechanisms of hypertension in obesity. *SNS* sympathetic nervous system

the renin–angiotensin–aldosterone system (RAAS) is sodium and water retention, which raises BP. Also contributing to the reduced blood flow through the kidney is direct compression of the parenchyma by perinephric fat [44], which encourages sodium reabsorption and contributes to higher BP. This phenomenon occurs even in the absence of signs of glomerular sclerosis or chronic kidney disease.

Increased levels of leptin, a hormone produced by adipose tissue, have been associated with elevated BP, a relationship that to a large extent is mediated by BMI and, as with hyperinsulinemia, has effects on the SNS [46]. This is illustrated in a recent cross-sectional study of 9,000 children in Indiana, which demonstrated that overweight children (BMI >85th percentile) had significantly higher leptin levels than children of normal weight; BP percentiles of the overweight children were also higher than those of the normal-weight children [32]. Conversely, obese individuals produce less adiponectin, another antiatherogenic, cardioprotective hormone made in adipose tissue that has been shown to inversely correlate with BP parameters in obese children and adolescents [47]. The proinflammatory cytokines and oxidative stress produced in obesity probably contribute to vascular endothelial dysfunction, impairing the local vasodilatory response, thereby increasing BP because of increased peripheral resistance.

Obese children with sleep-disordered breathing (apnea, hypopnea) are at an even higher risk of developing hypertension, especially at night. This is probably also related to the activation of the SNS due to intermittent hypoxia. Furthermore, SNS activation via multiple other obesity-related mechanisms and morbidities may contribute to a higher BP in obese children; these include but are not limited to the proinflammatory state created by cytokines such as increased IL-6 production, which in turn results in an acute phase response. In addition, the SNS plays a role in energy balance and metabolic syndrome as fasting suppresses, and meal ingestion induces, SNS activity [48]. Weight loss reduces SNS overactivity in obesity, which may partly explain the lower BP in response to dieting [49]. Central fat distribution is also associated with disturbances in the hypothalamic–pituitary–adrenal axis, suggesting that a disturbed axis might be implicated in the development of the metabolic syndrome [50].

Finally, it is important to acknowledge the important role played by the RAAS in obesity hypertension. Adipocytes contain all components of the RAAS locally, and all components of the RAAS have been shown to be increased in obesity, including angiotensinogen [44, 51]. The SNS activation discussed earlier likely plays a role in increasing the activity of the RAAS in obesity. Patient-level data in pediatric studies have not been clear, however. Although a significant correlation was seen between BMI and plasma renin activity (PRA) in a population of obese adolescents [52], ambulatory BP levels did not correlate with PRA. In an earlier study, however, we did show that BP was more severe in primary hypertension patients with high PRA compared with those with low PRA [36]. Additional clinical and experimental studies will be needed to better elucidate the relationships between components of the RAAS and BP in obese children.

Conclusions

It should be clear from the preceding discussion that the epidemiology of hypertension in childhood and adolescence is shifting owing to the worldwide obesity epidemic: hypertension is more frequent, and primary hypertension has become the predominant cause seen in the young, even at referral centers. It has been predicted that given the current obesity trends, there will be an epidemic of early-onset adult cardiovascular disease [53, 54]. As pediatricians, we understand the importance of prevention. In addition to identifying and treating obesity-related hypertension in children and adolescents, efforts to prevent the impending epidemic of adult cardiovascular disease must also be instituted, ideally in young school-aged children (or perhaps even earlier), before obesity-related co-morbidities develop.

Multiple choice questions (answers are provided following the reference list)

1. You are asked to evaluate a 5½-year-old girl for elevated BP. Her prior BP readings are consistent with stage 1 hypertension. Her height, weight, and BMI are all at the 99th percentile for age. Her physical examination is remarkable only for abdominal striae. Which of the following diagnostic studies would be least appropriate at this time?
   a) Urine microalbumin to creatinine ratio
   b) Electrolytes, BUN, and creatinine
   c) Complete renal ultrasound
   d) Fasting glucose and lipid panel
2. Current data indicate that in less developed countries, obesity-related hypertension need not be considered in the differential diagnosis of a hypertensive adolescent.
   a) True
   b) False
3. An obese adolescent with elevated blood pressure has undergone 24-h ambulatory BP monitoring. Salient findings include: elevated mean awake SBP, normal mean awake DBP, normal mean sleep SBP and DBP, SBP dipping 19 %, DBP dipping 12.5 %, mean awake heart rate 101, mean sleep heart rate 85. Which of the following mechanisms is most likely to account for this patient's hypertension?
   a) Volume expansion
   b) Elevated plasma renin activity
   c) Increased CNS sympathetic output
   d) Parenchymal renal disease
4. Population data from the United States have demonstrated several changes affecting childhood blood pressure over the past 1–2 decades. Which of the following statements best summarizes those changes?
   a) Absolute BP levels have increased among white children and the prevalence of hypertension among Mexican–American children has remained stable.
   b) Absolute BP levels have increased among all groups of children, with the greatest changes seen among white children
   c) Absolute BP levels have remained stable among all groups of children, but the prevalence of prehypertension has increased markedly
   d) Absolute BP levels and the prevalence of hypertension have varied among children of different racial and ethnic groups
5. Adipocytes are just as likely to contribute to hypertension in obese children as are juxtaglomerular cells.
   a) True
   b) False

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Answers:

1. a
2. b
3. c
4. d
5. a