The Role of Obesity, Salt and Exercise on Blood Pressure in Children and Adolescents
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Abstract and Introduction
Abstract
The increasing trends of blood pressure (BP) in children and adolescents pose great concern for the burden of hypertension-related cardiovascular disease. Although primary hypertension in childhood is commonly associated with obesity, it seems that other factors, such as dietary sodium and exercise, also influence BP levels in children and adolescents. Several studies support that sympathetic nervous system imbalance, impairment of the physiological mechanism of pressure natriuresis, hyperinsulinemia and early vascular changes are involved in the mechanisms causing elevated BP in obese children and adolescents. Under the current evidence on the association of salt intake and BP, dietary sodium restriction appears to be a rational step in the prevention of hypertension in genetically predisposed children and adolescents. Finally, interventional studies show that regular aerobic exercise can significantly reduce BP and restore vascular changes in obese with hypertensive pediatric patients. This article aims to summarize previous studies on the role of obesity, salt intake and exercise on BP in children and adolescents.

Introduction
The prevalence of primary hypertension (HTN) in children and adolescents has been reported to have increased during the last few decades.[1] HTN awareness is currently increased, due to the easier detection and improved classification of HTN in the young.[2] Despite the difficulty in estimating the exact percentage of children with elevated blood pressure (BP), pediatric primary HTN is present in 1–5% of children and adolescents of all age groups.[3,4] Differences in race/ethnicity, variance in secondary HTN, sex-related changes, environmental and nutritional influences are all confounding factors in the estimation of prevalence.

The most important aspect of identifying HTN in the pediatric population is ‘BP tracking’, that means the association of high BP in childhood with elevated BP in adulthood.[5–7] With this concept, factors that affect BP in childhood, are likely to further influence the burden of HTN and cardiovascular disease in adults. The documented increasing prevalence of childhood obesity has accounted for the trends of elevated BP in children and adolescents. However, in the recent National Health and Nutrition Examination Survey (NHANES; 1988/1994 and 1999/2000), adjustment for obesity explain only 29% of the increase in systolic BP (SBP) and 12% in diastolic BP (DBP), suggesting that other factors, such as increased salt intake and low physical activity, may also affect BP trends over time.[8] This article aims to summarize previous studies on the role of obesity, salt intake and exercise on BP in children and adolescents.

Definition of Pediatric HTN
Hypertension in children and adolescents is defined as the average office SBP and/or DBP ≥95th percentile for gender, age and height on at least three occasions.[2] Pre-HTN is defined as the average office SBP and/or DBP levels ≥90th percentile, but <95th percentile, or if average BP levels ≥120/80 mmHg. Stage 1 HTN is defined as office SBP and/or DBP ≥95th percentile up to 99th percentile plus 5 mmHg, and finally stage 2 HTN as SBP and/or DBP ≥99th percentile plus 5 mmHg. Repeated BP measurements on separate visits are recommended for the diagnosis of HTN to avoid over-diagnosis of HTN, due to BP variability in children with BP ≥95th percentile.[4]

In children and adolescents no cohort data to relate BP levels with cardiovascular outcome are available. BP cut-off values are based on the statistical parameters of BP distribution in healthy children and adolescents. The BP percentiles specific for age, sex and height determined on the basis of data from children aged 1–17 years, who were participating in surveys in the 1970s and 1980s in the USA, are the
The usefulness of ambulatory blood pressure monitoring (ABPM) in assessing BP levels in an accurate and reproducible way has been demonstrated in numerous studies in children and adolescents.[10–16] HTN is defined by mean ambulatory BP values as mean 24 h, and/or daytime, and/or nighttime SBP and/or DBP ≥95th for sex and height. The combination of office BP measurements and ABPM enables the diagnosis of white-coat HTN (elevated office BP, but normal daytime ambulatory BP), masked HTN (elevated ambulatory BP combined with normal office BP) and nondipping status (≤10% decrease in BP during nighttime) in the pediatric population.[13,14,16–18] Moreover, ABPM is superior to office measurements in evaluating target organ damage.[18–23] HTN and pre-HTN defined by ambulatory BP mean values have been associated with increased left ventricular mass index and higher prevalence of left ventricular hypertrophy in a study including 124 consecutive children and adolescents, aged 5–18 years.[22] The 24-h pulse pressure has been reported to be predictive of cardiac damage in hypertensive children.[23] In addition, patients with masked HTN exhibited higher left ventricular mass indices than confirmed normotensives in adult and pediatric populations assessed with ABPM.[18,19]

**Childhood Obesity & BP Regulation**

The obesity epidemic has shared increasing interest during the last decades as one of the major causal factors of primary HTN and early onset of cardiovascular disease in the adult population.[24] The increasing prevalence of obesity in children and adolescents is alarming and demands tailored management due to the wide spectrum of comorbidities, including HTN, dyslipidemia, Type 2 diabetes mellitus and orthopedic and respiratory problems.[25,26] Childhood obesity is defined as BMI ≥95th percentile for age and sex or by international standards age- and sex-specific values corresponding to adult BMI of 30 kg/m2.[27,28] It is strongly and independently associated with elevated BP during childhood and tends to track into adulthood.[27] BP rises across the entire range of BMI values in children and adolescents. The risk for developing HTN in the obese pediatric population is three-times greater than in non-obese individuals.[26] The association between obesity, pre-HTN and HTN in children has been reported in a variety of ethnic and racial groups (Table 1). Studies using ABPM to assess the impact of obesity on BP in obese children and adolescents have shown significantly positive relations between obesity and ambulatory BP parameters, stronger with systolic BP variables.[29–31] White-coat HTN was also found to be more prevalent in obese compared with non-obese children.[18,29,31] Other measures of childhood adiposity, percent body fat and waist circumference are also correlated to BP.[30,32] Moreover, they could represent prognostic indices of BP levels in adulthood. In the Fels Longitudinal Study, childhood percent body fat was positively associated with adult BP in men and women, while childhood height-adjusted waist circumference was positively associated with adult BP in men only, with a stronger association for SBP than DBP values.[33]

Most of the pathophysiologic mechanisms of obesity HTN have been examined in animal and adult studies.[34] Several studies are also currently available providing insights into the mechanisms causing elevated BP in obese children and adolescents. Imbalance of the autonomic nervous system function has been demonstrated in obese children and adolescents. Sorof et al. found that in a school-based screening study, obese adolescents had the higher resting heart rate compared with non-obese hypertensive peers.[35] Obese children were also reported to have a higher heart rate and BP variability compared with non-obese children.[31,35–37] Martini et al. used power spectral analysis of heart rate variability and showed that an increase in heart rate and in BP was associated with parasympathetic heart rate control decrease in obese normotensive children.[36]

Obesity during the first two decades of life seems to restrict sodium excretion, leading to higher BP values. In 60 obese adolescents aged 10–16 years, elevated BP was directly associated with a volume-dependent increased stroke volume and was reduced with a low-sodium diet, suggesting that increased sodium sensitivity mediated a plasma volume-dependent increase of stroke volume and cardiac output, thereby increasing BP.[38] Lurbe et al. found that for same urinary sodium excretion level, obese children had a higher nocturnal SBP compared with lean children, proving evidence for a shift of pressure natriuresis to higher BP levels in obese children.[39] The interaction between sodium excretion and...
weight was negative, indicating that the rate of change of SBP by sodium unit is smaller for the obese than for the non-obese children.

Hyperinsulinemia correlates with high BP levels in children, adolescents and young adults.[40,41] In a study including 87 overweight and obese children and adolescents, a significant positive relationship was demonstrated between fasting insulin and Homeostasis Model Assessment Index (HOMA) with office, sleep SBP and heart rate, after adjusting for age and sex, a relationship that was not observed for awake SBP.[42] The early increment of nocturnal BP and heart rate associated with hyperinsulinemia was suggested to be a harbinger of HTN-related insulin resistance. In the presence of insulin resistance, overactivity of the central sympathetic nervous system has been demonstrated, contributing to increased peripheral resistance, reduced baroreceptor dysfunction, and increased sodium reabsorption in the kidney.[34] Finta et al. demonstrated that hyperinsulinemia that occurs in obese adolescents following an oral glucose tolerance test, results in urinary sodium retention.[43] However, in another study, Csabi et al. found that serum norepinephrine levels were significantly higher in obese children as compared with controls, and had a significant negative correlation with urinary sodium excretion, but hyperinsulinemia was not directly correlated with sodium excretion.[44]

Similar to adults, obese children also appear to be characterized by adverse changes in vascular health, which may also contribute to elevated BP levels seen in this population.[29,45–47] There is evidence that obesity is characterized by vascular inflammation, caused by an imbalance between the vasodilatory and vasoconstrictory substances produced in the endothelium.[34] Production of vasodilatory endothelial nitric oxide is impaired, while a variety of proinflammatory and inflammatory molecules, angiogenetic factors and acute phase reaction proteins are produced in the adipose tissue.[48] Kapiotis et al. measured flow-mediated dilation of the brachial artery and carotid intima-media thickness, as markers of early vascular changes, in 77 obese children. They also measured blood levels of high sensitivity C-reactive protein, IL-6, soluble intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin. Obese children had significantly higher levels of high sensitivity C-reactive protein, IL-6, E-selectin, lower peak flow-mediated dilation response and increased carotid intima-media thickness compared with controls.[49] Tounian et al. demonstrated lower arterial compliance, lower distensibility and lower endothelium dependent/independent function of the common carotid arteries in severely obese compared with lean children.[47] Weight loss has been reported to result in the reduction of forearm vascular resistance in obese adolescents.[50] Increased carotid intima-media thickness was positively correlated with BMI in several studies in obese normotensive and hypertensive children.[29,51,52]

Obesity in children born with low birthweight may associate with increased risk of HTN. The presence of intrauterine fetal growth retardation seems to affect BP later in life. In a study conducted by Lurbe et al., low birthweight was associated with high BP, greater BP variability and pulse pressure in a group of children and adolescents aged 10–18 years.[53] When low birthweight was combined with obesity during childhood and adolescence, the BP-raising effects were augmented.[53,54] Early stiffening of the arteries has previously been related to intrauterine fetal growth retardation.[55] Nevertheless, fast weight gain between infancy and childhood does not exhibit a greater significance for increases in BP than weight gained at any other age.[56]

Dietary Salt Intake & BP in Childhood
The International Study of Salt and Blood Pressure (INTERSALT) has provided strong evidence for the association between dietary sodium and elevated BP in adults, especially in Western societies.[57] Yanomamo Indians in the Amazon, who have a low-salt intake, present with a low average BP, no HTN and no positive slope of BP with age.[58] There is also substantial evidence that a reduction in salt intake lowers BP and can prevent HTN and adverse cardiovascular outcomes.[59,60] Most studies in children show that the average daily salt intake exceeds nutritional needs.[61] As dietary habits create nutritional patterns for the young population, contamination of foods rich in salt increases over time in modern societies, emerging the need for prevention strategies that will reduce sodium exposure in the young through dietary modification.

The effect of salt intake may begin early in life. A randomized trial, conducted among 476 Dutch newborn infants, studied the effect of low or normal sodium diets on BP. Infants fed with a low sodium diet had 2.1
mmHg lower SBP than those under a normal sodium diet at the age of 6 months.[62] A subset of these populations was re-examined 15 years later. SBP and DBP at adolescence were 3.6 and 2.2 mmHg lower, respectively, in subjects assigned to the low sodium compared with the control group.[63]

Most observational epidemiological studies on salt and BP in children showed a significant positive association between dietary sodium and BP. However, in a study among Spanish school children, urinary excretion of sodium did not correlate with BP, whereas bodyweight correlated directly with BP and salt intake.[64] The investigators assumed that the BP-raising effect of increased dietary sodium might not be seen until a certain age. Moreover, Howe et al. reported that dietary short-term sodium interventions, consisting of a 4-week high-salt diet following 4 weeks low-salt administration, had no significant alterations on BP levels in adolescents.[65] A more reliable estimation of the sodium effects on BP could possibly be seen after a longer time period of sodium restriction. Sinaiko et al. enrolled 13-year-old adolescents in a study of 3-year period sodium interventions. Adolescent girls receiving a low-salt diet, presented a decrease in urinary sodium excretion and a slight decrease in BP levels.[66] A recent meta-analysis of 13 controlled trials on salt reduction in children demonstrated that even a modest reduction in sodium intake causes immediate decreases in BP, and suggested that it may well lessen the subsequent rise in BP with age.[67] The changes in salt intake were assessed by 24-h urinary sodium in four trials, overnight urinary sodium in three trials, spot urinary sodium/creatinine ratio in two trials, spot urinary sodium in two trials, food diary in one trial and random 24-h urinary sodium in one trial. Among the 13 trials, ten were in children and adolescents and three were in infants. The median reduction in salt intake was 42% (interquartile range: 7–58%) in children and adolescents and 54% (interquartile range: 51–79%) in infants.

Individual variations in response to high or low sodium intake impact on BP define salt sensitivity or resistance. Children genetically predisposed to develop HTN, such as African–Americans, as well as those with a family history of HTN, more likely exhibit increased salt sensitivity.[68] Simonetti et al. described the highest prevalence of salt sensitivity in children with intrauterine fetal growth retardation, born small for gestational age.[69] In this study, salt sensitivity was defined if mean 24-h BP increased by 3 mmHg on a high-salt diet and was present in 37% of the low birthweight children. Kidney volume and length measured by ultrasound were reduced in low birthweight children and correlated with increased salt sensitivity, suggesting that a deficit of the normal nephron function in children with low birthweight, may lead to increased salt sensitivity and HTN. A similar relation of birthweight to salt sensitivity has been reported in adults.[70]

Several investigators examined the impact of salt sensitivity on the circadian variation of BP. Nondipping status, which is considered an early predictor of cardiovascular and renal complications, has been associated with increased salt sensitivity in hypertensive adults.[71,72] It is assumed that in individuals with high-salt sensitivity, sodium retention and diminished excretory capability leads to elevation in nighttime BP values. This nocturnal HTN compensates for diminished natriuresis during the daytime and enhances pressure natriuresis during the night. Studies with regard to nondipping pattern and salt sensitivity in children and adolescents are controversial. Salt sensitivity has been associated with nondipping status in salt sensitive normotensive black adolescents.[73] However, in a study conducted by Simonetti et al. normotensive children and young adults maintained normal nocturnal BP dipping independently of salt intake and sensitivity.[74] In the same study, a steeper downward slope of BP from daytime to nighttime was observed in salt-sensitive as compared with salt-resistant children and in both groups of adults. The findings of this study may show that a time interval is needed for blunted dipping to develop, as in children the excretory sodium capacity seemed less affected than in young adults with longer exposure to salt.

Salt sensitivity has been reported to involve endogenous ouabain, a modulator of the sodium pump in humans. In prehypertensive and hypertensive individuals, circulating levels of endogenous ouabain are not properly regulated in relation to sodium balance. The main mechanism of endogenous ouabain action, which has been described in animal models, may be an elevation in total peripheral resistance.[75,76] In normotensive rats, acute elevations in salt intake lead to impairment of the muscular arteriolar response to vasodilator agonists in 3 days.[77] The same effect was reported in normotensive and in reduced renal mass hypertensive rats receiving a high-salt diet for 4 weeks. In normotensive rats,
impairment of the vascular function was proportionate to the remodeling of the microvessel wall, so that the sodium sensitivity remained unchanged. In reduced renal mass hypertensive rats the effects on the structure of microvessels was greater and resulted in increased sodium sensitivity and HTN.[78]

Despite the major role that sodium plays in the development of HTN in children and adolescents, salt sensitivity should be characterized as one component of the whole spectrum of cardiovascular risk factors. Sensitivity to sodium or high-salt intake alone may not directly cause a hypertensive profile, but could be interrelated to other factors, such as family history of HTN, race and obesity, which altogether contribute to the development of HTN and an adverse cardiovascular profile.[79]

**Exercise & Prevention of HTN in Children & Adolescents**

Regular physical activity reduces the risk of cardiovascular disease morbidity and mortality, but also lowers BP and prevents the development of HTN.[80,81] In a population-based prospective cohort study over an 11-year follow-up period, the incidence of HTN was reduced by 28% in men and 35% in women who engaged in high levels of physical activity.[82]

An immediate reduction in BP occurs after an aerobic exercise session (postexercise hypotension). Several studies using ABPM demonstrated that the BP-lowering effects of exercise are most pronounced in people with HTN who engage in endurance exercise, with 24-h daytime BP decreasing by 5–7 mmHg after an isolated exercise session (acute) or following aerobic exercise training (chronic).[83] BP remains lower for the rest of the 24-h period after each 30-min period of moderate exercise (50% of maximal O2 uptake) with greater BP reductions for vigorous exercise (75% of maximal O2 uptake).[84] The mechanisms involved in the postexercise hypotension may involve the reduced activity of sympathetic nervous and renin–angiotensin–aldosterone systems.[85,86] Brownley et al. reported that 65% of the postexercise mean BP response difference could be accounted for by changes in sympathetic factors, with change in norepinephrine and pre-ejection period elongation being the single best predictors.[87] Restoration of balance in functions of the autonomic nervous system was proposed to serve as a possible exercise-dependent mechanism of BP reduction in obese children.[88] Moderate-intensity aerobic exercise has also been shown to augment endothelium-dependent vasodilation in humans through the increased production of nitric oxide.[89]

Data from a subset of the 1998–2002 NHANES survey, including 3110 healthy adolescents (aged 12–19 years) and 2205 adults (aged 20–49 years), revealed that cardiorespiratory fitness, estimated by the duration of a maximal treadmill exercise test, was inversely associated with the risk of developing HTN in both adolescents and adults.[90] Low fitness was identified in 33.6% of adolescents and 13.9% of adults. Lobelo et al. also found an excess cluster of cardiovascular risk factors including SBP in both overweight and normal weight adolescents with lowest quintile of cardiovascular fitness distribution.[91] SBP measured during exercise at the age of 9 years predicted resting SBP 6 years later in adolescent in healthy Danish children.[92] Decline in duration and intensity of physical activity was associated with higher SBP in 12-year-old adolescents followed longitudinally for 5 years. A decline of one session of moderate to vigorous exercise session per week each year of age was reported to result in 0.40 and 0.18 mmHg higher SBP in boys and girls, respectively, at the end of the follow-up period.[93]

Intervention studies showed that aerobic exercise training at an intensity of 70–80% of maximal fitness, 5 days per week, reduced SBP in hypertensive and obese adolescents.[50,94] However, a meta-analysis of 12 randomized controlled trials by Kelley et al. reported that exercise led to small, but not statistically significant, reductions in resting BP in children and adolescents.[95] The lack of statistical significance was attributed to the fact that the majority of the subjects were normotensive, as well as to the lack of strictly defined sedentary control group in most of the included studies. More recent data provide increasing evidence for the positive influence of regular aerobic exercise in resting and 24-h SBP in obese and hypertensive children and adolescents.[96–99] Apart from the positive effects on BP and HTN rate, Meyer et al. demonstrated that regular exercise, three-times per week, 60–90 min per day, over 6 months, improved early vascular changes as measured by flow-mediated dilation and carotid intima-media thickness.[99] In a similar study by Maggio et al. the beneficial effects on BP, BMI and arterial stiffness remained 2 years after the cessation of training in obese children, in a recently published follow-
up study.[98] The majority of the subjects maintained physical activity with further improvements of BP and arterial function.

Dietary supervision should be combined with regular physical activity, aiming to control BP, reduce extra weight, improve insulin sensitivity and establish a new lifestyle for children prone to developing HTN and cardiovascular disease. Children of parents with relatively high physical activity have been reported to be 5.8-times more likely to be active themselves than children of two inactive parents.[100] The main correlates of physical activity in a group of Singaporean adolescents were self-efficacy, enjoyment of physical activity, parental support and participation in sport teams.[101] Current recommendations for exercise in healthy children and adolescents include 30–60 min per day of moderate-to-vigorous physical activity at least three-times per week.[201] Moderate-to-vigorous-intensity exercise equals to 5–8 metabolic equivalents. This intensity should be maintained for a long duration of time to lower BP values in children with mild essential HTN (five-times per week for 30–60 min).[201] Ideal levels of physical activity should be calculated for each individual separately, in connection with the expected cardiovascular benefit from a greater oxygen consumption. Moreover, children should be encouraged to reduce time spent in sedentary activities, such as playing video games or watching television to less than 2 h per day.

Expert Commentary
All the previous points underline the need for targeted action against primary HTN in children and adolescents. At the same time, evaluation and reduction of comorbidity factors (obesity, high-salt intake and low physical fitness) is a primary goal of the antihypertensive therapy. Target-organ damage is evident in hypertensive pediatric patients even with mild HTN in the presence of comorbid factors. Obesity and elevated BP may act synergistically and lead to an increased total cardiovascular risk, starting in early childhood. Early arterial wall changes may be useful in predicting other cardiovascular complications of obesity over time. Moreover, in obese pediatric patients at greater risk of developing HTN and related outcomes, ABPM is more predictive of target organ damage, and should be performed in all overweight and obese children and adolescents with transient BP elevation. Given the influence that behavioral patterns of parents and family environments have on the development of the child's nutritional habits and lifestyle, the importance of health-promoting strategies in the young population becomes urgent in order to deal with the increasing burden of cardiovascular disease.

Five-year View
Research efforts should focus on the etiology and complexity of risk factors leading to childhood HTN. Although the role of obesity is well documented in the development of HTN, the effect of dietary salt needs to be evaluated in prospective studies controlling for other risk factors and in different populations. Most importantly, longitudinal studies are needed to define the BP levels in children related to adverse outcomes later in life, in order to increase our knowledge on the total cardiovascular risk in the young and further adjust BP-lowering interventions. With regard to the role of exercise as a countermeasure against the development of high BP in children and adolescents, further research is required on the long-term results of exercise in obese, hypertensive children and adolescents, and in those with markers of extreme obesity and an increased cardiovascular risk profile.

Sidebar
Key Issues
- The prevalence of primary hypertension (HTN) in children and adolescents has been reported to increase over the years.
- Factors affecting blood pressure (BP) in childhood such as obesity, increased dietary salt and low physical activity are likely to further influence the burden of HTN and cardiovascular disease in adults.
- Hyperinsulinemia and reduced sodium excretion are associated with elevated BP in obese children.
- Obese children present adverse vascular changes that may contribute to elevated BP levels.
- Fast weight gain between infancy and childhood is related to increased prevalence of HTN.
- Most observational epidemiological studies on salt and BP in children show a significant positive association between dietary sodium and BP.
- Children genetically predisposed to develop HTN, such as African–American individuals, as well as those with family history of HTN, are more likely to exhibit increased salt sensitivity.
Low cardiorespiratory fitness is inversely associated with the risk of developing HTN in adolescents.

Current recommendations for exercise in healthy children and adolescents include 30–60 min per day of moderate-to-vigorous physical activity at least three-times per week.

References
• This meta-analysis of salt reduction in children demonstrates that a modest reduction in salt intake causes immediate falls in BP suggesting that, if continued, it may well lessen the subsequent rise in BP with age.
Website
201. US Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
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