Obesity Hypertension in Children
A Problem of Epidemic Proportions

Jonathan Sorof, Stephen Daniels

Abstract—Obesity has become an increasingly important medical problem in children and adolescents. In national surveys from the 1960s to the 1990s, the prevalence of overweight in children grew from 5% to 11%. Outcomes related to childhood obesity include hypertension, type 2 diabetes mellitus, dyslipidemia, left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, orthopedic problems, and psychosocial problems. Once considered rare, primary hypertension in children has become increasingly common in association with obesity and other risk factors, including a family history of hypertension and an ethnic predisposition to hypertensive disease. Obese children are at approximately a 3-fold higher risk for hypertension than nonobese children. In addition, the risk of hypertension in children increases across the entire range of body mass index (BMI) values and is not defined by a simple threshold effect. As in adults, a combination of factors including overactivity of the sympathetic nervous system (SNS), insulin resistance, and abnormalities in vascular structure and function may contribute to obesity-related hypertension in children. The benefits of weight loss for blood pressure reduction in children have been demonstrated in both observational and interventional studies. Obesity in childhood should be considered a chronic medical condition that is likely to require long-term management. Ultimately, prevention of obesity and its complications, including hypertension, is the goal. (Hypertension. 2002;40:441-447.)

Key Words: hypertension, obesity ■ children ■ epidemiology ■ cardiovascular diseases ■ risk factors

Obesity has become an increasingly important medical problem in children and adolescents. Many of the outcomes associated with obesity that were previously thought of as diseases of adults are now affecting children as well. Outcomes related to childhood obesity include hypertension, type 2 diabetes mellitus, dyslipidemia, left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, and orthopedic problems (such as slipped capital-femoral epiphysis), as well as social and psychological problems. Obesity is also the most common nutritional problem among children in developed countries. This epidemic of pediatric obesity has resulted in great concern regarding the management of obesity and its complications. Although prevention would be an optimum strategy, it may be difficult to identify children at risk of obesity before they become overweight. Even with appropriate preventive approaches, it is likely that many children will become overweight and require treatment to prevent the long-term sequelae of obesity, such as cardiovascular morbidity and mortality. In concert with the increasing prevalence of obesity in children, pediatric hypertension has undergone an epidemiological shift. The conventional wisdom has been that hypertension in children is a relatively rare condition most commonly associated with renal disease. In actuality, secondary hypertension in children resulting from renal disease has become far less common than that related to primary (ie, essential) hypertension. In a large pediatric hypertension practice, the typical patient demographic has evolved into an otherwise healthy adolescent with obesity and some combination of the cardiovascular risk factors associated with obesity, including a family history of hypertension and an ethnic predisposition to hypertensive disease.

The general topic of obesity hypertension has previously undergone comprehensive review. The goal of this current review will be to focus specifically on available data on the epidemiology, pathophysiology, sequelae, and management of obesity-related hypertension in children.

Epidemiology
In the United States, the prevalence and severity of overweight status is clearly increasing among children. In national surveys from the 1960s to the 1990s, the prevalence of overweight in children grew from 5% to 11%. Furthermore, Morrison et al showed that much of the increase in body mass index (BMI) in grade school–aged children between the
1970s and 1990 occurred in children between the 50th to 100th percentiles. This increase in the severity of obesity has also translated into an increase in the prevalence of outcomes such as type 2 diabetes mellitus and hypertension. A hospital-based study by Pinhas-Hamiel et al. reported a 10-fold increase in the prevalence of newly diagnosed type 2 diabetes mellitus in adolescents from 1982 to 1994. The average BMI in this group was 37 kg/m². Similarly, Leupker et al. found a concordant increase in BMI and systolic blood pressure in middle school students, aged 10 to 14 years, from 1986 to 1996.

This association between obesity and hypertension in children has been reported in numerous studies among a variety of ethnic and racial groups, with virtually all studies finding higher blood pressures and/or higher prevalences of hypertension in obese compared with lean children. The most comprehensive study by Rosner et al. pooled data from 8 large US epidemiological studies involving over 47,000 children to describe the blood pressure differences between black and white children in relation to body size. Irrespective of race, gender, or age, the risk of elevated blood pressure was significantly higher for children in the upper compared with the lower decile of BMI, with an odds ratio of systolic hypertension ranging from 2.5 to 3.7. Freedman et al. reported that overweight children in the Bogalusa Heart Study were 4.5 and 2.4 times as likely to have elevated systolic blood pressure and diastolic blood pressure, respectively. Sorof et al. found a 3 times greater prevalence of hypertension in obese compared with nonobese adolescents in a school-based hypertension and obesity screening study.

The early clinical course of obesity hypertension appears to be characterized by a preponderance of isolated systolic hypertension (systolic hypertension without diastolic hypertension). Data from a recent multicenter trial of an antihypertensive medication in children showed that among all 140 subjects who enrolled in the trial, 37% had isolated systolic hypertension alone. The prevalence of isolated systolic hypertension was 50% (25/50) in obese subjects compared with 30% (27/90) in nonobese subjects \( (P=0.02) \). In the school-based screening for hypertension and obesity by Sorof et al., the prevalence of isolated systolic hypertension among adolescents who were obese and had blood pressure above the 95th percentile on a single set of measurements was 94%. Because isolated systolic hypertension has been shown to be a major risk factor for cardiovascular morbidity and mortality in adults, further investigation of the causes and interventions for this pattern in children is clearly needed.

The classification of weight status into dichotomous categories of “obese” or “nonobese” is clinically useful for characterizing the overall risk of hypertension from obesity. However, these arbitrary percentile-based categories of body habitus preclude more detailed examination of the risk relationship between adiposity and blood pressure. In fact, the risk of hypertension in children increases across the entire range of BMI values and is not defined by a simple threshold effect. Rosner et al. reported a linear increase in the prevalence of diastolic hypertension in children of all race, gender, and age combinations as BMI increased across the

Figure 1. Distribution of BMI percentiles and the prevalence of hypertension within each BMI percentile category. Values above bars indicate number of children within each BMI category. NML indicates normotensive; HTN, hypertensive.

“normal” range. Similarly, Sorof et al. found an increased prevalence of systolic hypertension (based on a single set of measurements) as BMI percentile increased from the 5th to the 95th percentile (Figure 1). Among all demographic and clinical factors analyzed, BMI was most strongly associated with hypertension.

The dichotomous classification of blood pressure status into “hypertensive” or “normotensive” is similarly restrictive. Blood pressure is a continuous variable that is positively correlated with cardiovascular risk across the entire blood pressure range. As an example, studies of normotensive and hypertensive children have reported that blood pressure and left ventricular mass index are positively associated across a wide range of blood pressure values. Furthermore, elevated left ventricular mass may be present even in children whose blood pressure values fall within the so-called “normotensive” range. Although a child’s current blood pressure may fall within the population-based range of normality, a previously undetected pattern of relative increases in blood pressure across percentile lines over time may still effectively render that patient “hypertensive.”

Nonetheless, many health care providers underdiagnose hypertension in children. Unlike in adults, in whom the definition and severity of hypertension are defined by straightforward threshold values based on the risk of outcomes, children require a separate threshold of blood pressure normality at each stage of physical maturity because of the normal age and height-related rise in blood pressure throughout childhood. The most recent Update from the Task Force on Hypertension Control in Children and Adolescents provided population-based percentiles for blood pressure values in children adjusted for age, gender, and height. Values that exceed the 90th and 95th percentiles are defined as “high normal blood pressure” and “hypertension,” respectively. Thus, the identification of the blood pressure threshold for hypertension in a child first requires determination of height percentile, followed by interpretation of a dense table of
blood pressure values with a separate threshold for each combination of gender, age, and height percentile. It is important to note that there are no normative blood pressure standards that account for weight or BMI in children. There is compelling evidence that overweight status and elevated blood pressure are closely related and synergistically increase cardiovascular risk. Adjustment of blood pressure norms based on increased weight would therefore inappropriately control for the pathologic influence of overweight on blood pressure.

Because these tables are not always used in everyday practice, mild-to-moderate hypertension may go unrecognized. As an example, although an average-sized 10-year-old boy with a persistent systolic blood pressure of 120 mm Hg might not create concern for many primary care physicians, this value exceeds the 95th percentile and thus meets the criteria for hypertension. Although helpful as a guide for the determination of normality, this "statistical" definition of hypertension in children based on population percentiles must ultimately be replaced by an evidence-based definition that links specific levels of blood pressure with outcome.

The accurate measurement of blood pressure in obese children may be particularly challenging because of the absence of blood pressure cuffs that are of appropriate length and width for the upper arm of a small obese patient. Larger-than-appropriate cuff size can give falsely low measurements, whereas a smaller one can give falsely high readings.25,26 This issue is of particular importance in children because of significant differences in arm sizes at various ages. The most important issue for measuring blood pressure in the obese is choosing the correct cuff-width:arm-circumference ratio.27 The most recent Update24 to the Task Force recommends that an appropriate cuff size should have a bladder width that is approximately 40% of the arm circumference midway between the olecranon and the acromion processes (Figure 2).

Pathophysiology

Although the majority of data on the pathophysiology of obesity hypertension are derived from studies of animals and adults, the mechanisms of obesity hypertension have been studied in children as well. Most studies of children have focused on investigation of 3 main pathophysiological mechanisms: disturbances in autonomic function, insulin resistance, and abnormalities in vascular structure and function. Although obesity-induced hypertension is likely due to an overlap or combination of these factors,28 systematic review of the data consistent with each mechanism is useful for understanding how they may contribute to the early stages of the disease process in children.

The link between obesity and hypertension may be mediated in part by sympathetic nervous system (SNS) hyperactivity. This state of hyperactivity may include cardiovascular manifestations such as increased heart rate and blood pressure variability, neurohumoral manifestations such as increased levels of plasma catecholamines, and neural manifestations such as increased peripheral sympathetic nerve traffic. Consistent with the SNS hyperactivity hypothesis, the Bogalusa Heart Study reported that, in a biracial group of children, resting heart rate was positively correlated with blood pressure and subcapsular skinfold thickness29 and a hyperdynamic cardiovascular state was positively associated with several measures of obesity.30 Similarly, Sorof et al14 reported from school-based screening for obesity and hypertension that obese hypertensive adolescents had the highest resting heart rate and nonobese normotensive adolescents had the lowest heart rate (Figure 3). When the analysis was restricted to only those who were hypertensive, a higher heart rate was observed in the obese compared with nonobese adolescents. Rocchini et al31 found that weight loss, with or without exercise, resulted in a significant reduction in heart rate in obese adolescents.

Obese children are also reported to have increased heart rate variability32 and blood pressure variability14 compared with nonobese children. Evidence suggests that the increased heart rate variability in obese children may be due to an altered balance between parasympathetic and sympathetic activity and not due exclusively to increased sympathetic activity. Using time- and frequency-domain heart rate variability analysis, 24-hour blood pressure and heart rate monitoring in obese normotensive children has shown an increase
in heart rate and in blood pressure associated with decreased parasympathetic heart rate control.\textsuperscript{33} Furthermore, physical training in obese children appears to alter autonomic function by reducing the ratio of sympathetic to parasympathetic activity.\textsuperscript{34} These data suggest that autonomic function has an important mediating role in the pathogenesis of obesity hypertension in children as well as in adults.

Insulin resistance has been implicated in the pathogenesis of obesity-related hypertension in children. Several studies have reported positive associations between fasting insulin levels and resting blood pressure in obese children and young adults.\textsuperscript{35–40} Nonetheless, this association does not necessarily indicate causation. Lugbetti et al\textsuperscript{41} studied 350 obese children who were categorized as hypertensive or normotensive. Although insulin was significantly higher in hypertensive than in normotensive children, the difference was not clinically relevant. Furthermore, insulin explained only a small amount of systolic and diastolic blood pressure variance, which disappeared after accounting for the confounding effects of age, weight, or other anthropometric dimensions. Weight loss in obese adolescents has also been shown to result in reductions in serum insulin levels and blood pressure\textsuperscript{41,42} and to render previously salt-sensitive individuals insensitive to the hypertensive effects of salt-loading.\textsuperscript{43} Based on these data, it has been suggested that the insulin resistance associated with obesity may prevent insulin-induced glucose uptake but leave the renal sodium retention effects of insulin relatively preserved, thereby resulting in chronic volume overload and maintenance of blood pressure elevation. However, Csabi et al\textsuperscript{44} found no relationship between insulin levels and reduced sodium excretion in obese children. Thus, a causal role of insulin resistance in the pathogenesis of obesity hypertension remains uncertain.

Altered vascular structure and function may also contribute to the pathogenesis of obesity hypertension. Ultrasound of the carotid artery has demonstrated increased intimal-medial thickness in diabetic children\textsuperscript{45,46} and children with familial hypercholesterolemia,\textsuperscript{47–49} compared with normal controls. In addition, increased vascular compliance has been reported in diabetic children\textsuperscript{50} and children with familial hypercholesterolemia.\textsuperscript{51} Similar vasculopathy has been found in obese children, in whom less severe metabolic disturbances such as glucose intolerance and dyslipidemia are common. Tounian et al\textsuperscript{52} reported lower arterial compliance, lower distensibility, and lower endothelium-dependent and -independent function in severely obese compared with control children. Similarly, Rocchini et al demonstrated decreased maximal forearm blood flow and increased minimum forearm vascular resistance in obese adolescents,\textsuperscript{53} which was improved after weight loss.\textsuperscript{54}

Although these data have provided insight into the potential mechanisms of obesity hypertension in children, truly mechanistic studies illustrating the pathophysiology of the early stages of the disease process have yet to be performed. To some extent, the vulnerability of the pediatric population from a research standpoint has been a barrier to performing studies such as neurography to measure peripheral sympathetic nerve traffic or interventional studies such as hyperinsulinemic euglycemic clamping. However, the acuity of the problem would argue for an expanded role for mechanistic studies in children to identify therapeutic interventions that may interrupt the disease process before the establishment of potentially irreversible sequelae.

**Cardiovascular Risk Factors and Complications**

The complications of obesity that are associated with cardiovascular disease include hypertension, dyslipidemia, insulin resistance, glucose intolerance, type 2 diabetes mellitus, left ventricular hypertrophy, and pulmonary hypertension resulting from obstructive sleep apnea.\textsuperscript{55} Many of these outcomes of obesity have traditionally been viewed as problems of adulthood. However, further study has revealed that many of these abnormalities may begin in childhood and adolescence.

Obesity in children has been associated with the development of early myocardial changes and coronary and carotid artery pathology. Kortelainen evaluated the autopsies of 210 children aged 5 to 15 years who had suffered a violent death.\textsuperscript{56} Ponderal index was a significant predictor of heart weight and the presence of coronary artery intimal fatty streaks. Similarly, Berenson et al\textsuperscript{57} demonstrated in the Bogalusa Heart Study that children and young adults who died primarily of trauma showed an association between BMI, systolic blood pressure, diastolic blood pressure, and the presence of fatty streaks and fibrous plaques in the aorta and coronary arteries at autopsy. Gidding et al\textsuperscript{58} studied by electron beam computed tomography 29 patients aged 11 to 23 years with familial hypercholesterolemia to evaluate the presence of coronary artery calcium. Coronary artery calcium deposits were found in 7 of 29 subjects and were associated with increased body mass index. Sorof et al\textsuperscript{59} measured carotid intimal-medial thickness by duplex vascular ultrasound in children and adolescents with essential hypertension to assess for evidence of early arterial changes. Carotid intimal-medial thickness was positively correlated with weight, BMI, and left ventricular mass index, but not with height or age.

Left ventricular hypertrophy has been shown to be an independent risk factor for cardiovascular disease morbidity and mortality.\textsuperscript{60} In children and adolescents, left ventricular mass is determined by body size, assessed both by growth (height) and weight (adiposity). Urbina et al\textsuperscript{61} reported that the major factor influencing left ventricular mass in the Bogalusa Heart Study was linear growth determined by height, but that measures of ponderosity were also significant determinants of LVM. Daniels et al\textsuperscript{62} reported that lean body mass was the strongest determinant of LVM, but that fat mass and systolic blood pressure were also significant predictors of LVM. In adolescents with essential hypertension, Daniels et al\textsuperscript{62} found severe LVH in 14% of subjects, with greater body mass index one of the major factors associated with increased LVM. A recent study of 115 children undergoing evaluation for hypertension found an overall prevalence of LVH of 38%.\textsuperscript{63} This shows that LVH can occur early in the course of hypertension in young individuals. Patients with LVH were heavier and had greater BMI than those without LVH, and LVM was positively correlated with BMI. These findings suggest that the combination of obesity, hypertension, and other risk factors for cardiovascular disease presents a par-
particularly adverse profile for ultimate cardiovascular outcomes.

Obesity early in life appears to increase the likelihood of clustering of cardiovascular risk factors. In a study of adolescent girls, Morrison et al. found that almost 11% of overweight white girls and 65% of overweight black girls had three cardiovascular risk factors compared with an expected frequency of 0.8%. Similar findings were reported for boys. The distribution of fat may also be important. Daniels et al. evaluated the effects of fat distribution on risk factors for cardiovascular disease in adolescents. A more central deposition of fat (android pattern) was associated with elevation of triglycerides, decreased HDL cholesterol, increased systolic blood pressure, and increased LV mass. These relationships persisted after controlling for other variables such as age, race, gender, and height. The most compelling evidence of cardiovascular risk factor clustering in youth comes from the Bogalusa autopsy study, in which subjects with 0, 1, 2, and 3 or 4 risk factors had, respectively, 19.1%, 30.3%, 37.9%, and 35.0% of the intimal surface covered with fatty streaks in the aorta.

Management

Most interventions for pediatric obesity have focused on behavioral approaches to diet and physical activity to address the main components of energy balance. Although these approaches have been shown to have both short- and long-term beneficial effects on BMI in selected patients, such success has not been uniform. This management approach is very labor intensive and is often not covered by medical insurance. Other dietary approaches which have been tried include the very low calorie diet and the protein-modified fast. Although these dietary approaches can be effective in selected patients, they have also been associated with important adverse effects. Surgical approaches have been used in morbidly obese adolescents but are clearly not appropriate for a large number of patients.

The role of pharmacological management in the management of pediatric obesity has been controversial. The history of pharmacological treatment of obesity in adults is replete with problems, and there have been few well-controlled studies to show that the available drugs are well tolerated and effective for use in obese children. Many of the drug treatments that have been tried in adults have resulted in complications such as with amphetamines and fenfluramine/dexfenfluramine. This history has reinforced the debate regarding whether medications should be used to treat obesity except under the most extreme circumstances. On the one hand, obesity is a chronic problem requiring long-term management and potentially long-term exposure to the adverse effects of medications, an issue of particular concern in growing and developing children. On the other hand, evidence for the benefits of weight loss on blood pressure in children may tilt the risk-benefit balance in favor of a more aggressive management approach for the prevention of future cardiovascular disease. One medication that is currently being evaluated for treatment of obesity in adolescents is sibutramine, an inhibitor of the reuptake of serotonin and norepinephrine. However, the safety and efficacy of sibutramine in patients under 16 years of age is still unknown. Furthermore, sibutramine may be associated with increased blood pressure in some patients and is not recommended for use in patients with a history of hypertension. Orlistat is a gastrointestinal lipase inhibitor that may hold promise for safe and effective pharmacological treatment for childhood obesity.

The benefits of weight loss on blood pressure reduction in children have been investigated both in observational and interventional studies. In a retrospective study based on a 10-year period of observation, Clarke et al. reported that children whose ponderosity increased over that period had a relative increase in blood pressure by 18 percentiles compared with their peers, whereas children whose ponderosity decreased had a relative reduction in blood pressure by 13 percentiles. The positive effect of weight loss on blood pressure in children has also been demonstrated in several interventional studies. One of the first such studies by Brownell et al. reported blood pressure reductions of up to 16/9 mm Hg in obese children who achieved significant weight reduction after 16 months of dietary counseling. Figueras-Colon et al. found that blood pressure was significantly reduced compared with baseline at all points of a study comparing 2 hypocaloric dietary modifications in obese children. Wabitsch et al. reported a blood pressure reduction of 9/5 mm Hg associated with a weight reduction of 8.5 kg after a 6-week dietary intervention in obese adolescent girls. Similarly, Gallistl et al. reported an 8/7 mm Hg blood pressure reduction associated with weight loss of 3.9 kg after a 3-week diet and exercise program in obese children.

Although these studies suggest that blood pressure reductions are induced by weight loss in obese children, each is limited by the absence of a matched control group to show that the blood pressure reduction was directly attributable to weight loss. The only controlled trial to date was performed by Rocchini et al. who randomized overweight adolescents to 3 interventions over a 20-week period: diet alone, diet plus exercise, and control (no intervention). Changes in systolic blood pressure from baseline in the diet plus exercise group, diet alone group, and control group were −16 mm Hg, −10 mm Hg, and +4 mm Hg, respectively. This latter study provides the most definitive evidence that weight loss, particularly in conjunction with exercise, can be beneficial in the management of obesity hypertension in children. However, the long-term benefits of weight loss on blood pressure remain to be defined because it is unknown whether the decline of blood pressure observed during acute weight loss is maintained.

Perspectives

The prevalence and severity of obesity is increasing in children and adolescents. These observations suggest that the trend of decreasing cardiovascular disease in adults observed over the past 50 years may be reversed as the current population of overweight children and adolescents become adults. At present, treatment for all overweight children and adolescents can be recommended based on available data. However, the methods used to achieve weight management remain controversial. It seems appropriate to reserve pharmacological therapy for children most severely affected by
Obesity and its sequelae. It is also appropriate to reserve such therapy for those who have failed or have had only modest success with behavioral therapy directed at dietary modification and increased physical activity. The presence of ongoing obesity-related outcomes such as hypertension, diabetes mellitus or impaired glucose tolerance, and dyslipidemia may increase the rationale for more aggressive therapy. Ultimately, multiple therapeutic strategies may be necessary to achieve the desired goal.

Obesity in childhood should be considered a chronic medical condition and, thus, is likely to require long-term treatment. Public health initiatives to educate community leaders and health care providers may prove instrumental in stemming the evolving epidemic of pediatric obesity and its complications. In addition, the scope and acuity of the problem facing our youth suggests that substantial research is needed that is focused on the mechanisms of hypertension related to obesity in the pediatric population. Such research will serve as the basis for future guidelines for prevention and treatment of obesity hypertension.

References


