Recent Developments in Pediatric Hypertension: Emphasis on Epidemiology, Etiology and Pathogenesis

Sami A Sanjad

Professor of Pediatrics and Nephrology, Department of Pediatrics and Adolescent Medicine, American University Medical Center, Beirut, Lebanon

Abstract
Hypertension in children was considered, until recently, to be secondary to renal, cardiovascular or endocrine etiology. During the past 2 decades, however, a substantial number of children aged 6 to 20 years have been diagnosed with primary or essential hypertension. The incidence of hypertension in children and adolescents appears to be on the rise. This is attributed at least in part to an increased prevalence of overweight and obesity in this population. Essential hypertension in childhood is a diagnosis arrived at by excluding the known causes of secondary hypertension. This paper reviews hypertension in children and adolescents with emphasis on the epidemiology, etiology and pathogenesis as well as the evaluation and management of the hypertensive child.

Keywords: Hypertension; Primary Hypertension; Secondary Hypertension; Antihypertensive Medications; Obesity

Introduction
Hypertension (HT) is one of the leading causes of adult morbidity and mortality with more than 1 billion affected globally. In the US almost one third of the adult population (age 18 and over) are hypertensive, but only 75% are actually receiving treatment and among these, only one half are well controlled [1]. Several studies, including a recent meta-regression analysis, indicate beyond doubt that blood pressure (BP) in childhood tracks into adulthood [2,3] thus making it imperative to diagnose and treat HT in childhood before cardiovascular complications and target organ damage occur. The traditional teaching was that HT in children had a renal or secondary etiology until proven otherwise. In the last 2 decades, with the advent of 24-hour ambulatory blood pressure monitoring (ABPM) in children, new data have emerged that allows us to better diagnose and quantify HT in the pediatric population. In our experience, ABPM is a useful tool in the diagnosis of arterial HT in children and adolescents and is helpful in identifying patients with white coat HT detected with casual BP measurements. Thus, it has been shown that a substantial number of children aged 6 to 18 years are now diagnosed with primary or essential HT [4-7].

Definition and Classification of Childhood Hypertension
Unlike adults, where a single BP level defines HT, the highest percentiles of BP specific to age, gender, and height continue to be used to define high BP throughout childhood.

The "Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents" classifies pediatric HT as follows (8):

Normal BP is defined as systolic and diastolic BP less than the 90th percentile. Prehypertension, when BP is between 90th and 95th percentile, or if BP exceeds 120/80 even if the reading is less than the 90th percentile.

Stage 1 HT is defined as an average systolic or diastolic BP of greater than or equal to the 95th -but less or equal to the 99th percentile for age and sex plus 5 mmHg.

Stage 2 HT is defined when BP is greater than the 99th percentile plus 5mmHg.

Epidemiology
Following the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in 2003, both systolic and diastolic BP thresholds for diagnosing HT were lowered significantly [7]. In addition, it has been shown recently that BP in children and adolescents seems to be increasing over the past 2 decades. This is attributed at least in part to an increased prevalence of overweight and obesity in this population [9-11]. A more precise characterization of individual BP is found when one averages multiple measurements taken over weeks to months. The likelihood of identifying a secondary cause of HT is directly related to the severity of HT and inversely related to the child’s age. Since a significant number of children are now being diagnosed with essential HT, it is appropriate to dedicate some discussion to this entity and review the epidemiology and current theories concerning its etiology and pathogenesis. Blood pressure variations are known to be influenced by many clinical parameters such as age, gender, weight, height and posture. In addition, normal diurnal fluctuation, changes in physical activity as well as emotional stress are important variables that can make...
The prevalence of HT in children has more than doubled in the past 20 years. This increased prevalence is not limited to the developed and developing countries only but appears to be a global phenomenon reaching 4-5%. Prehypertension prevalence in children is as high as 10%. The relationship of HT to overweight and obesity has already been alluded to and documented in several studies from North America, Europe and Asia [10-14]. Recently Hansen and colleagues analyzed the medical records of 507 hypertensive and pre-hypertensive children and adolescents from a cohort of 14000 participants from Northeast Ohio over a seven year span (3.6%). All these children visited an outpatient clinic at least three times during the study period. They found that 376 patients (74%) had undiagnosed HT and that only 80 patients (15.8%) had a correct HT diagnosis. Seven participants had undiagnosed stage 2 HT. Ironically, the data to make the diagnosis of HT or prehypertension was present in the patients’ records and yet these were missed [12]. The increasing epidemic of childhood obesity, combined with sedentary life styles, has contributed significantly to childhood HT. Epidemiologic studies indicate that about 30% of obese children have HT. Both HT and obesity are common preventable disorders facing pediatric clinicians. Thus, in a study by Sorof and Daniels the authors showed that there is a linear increment in the prevalence of HT as BMI percentiles increased. It was shown that when the BMI percentile was below 25%, the prevalence of HT was between 5-6%. In subjects with BMI percentiles at 90% and 95%, the prevalence rose to 23% and 34% respectively (fig 1) [13]. Moreover, Couch and Daniels demonstrated that when obese patients achieved a BMI reduction of 8-10% there was a corresponding decline in BP in the range of 8 to 16 mm Hg [14].

Etiology and Pathogenesis of Hypertension
Primary or Essential HT

The diagnosis of primary HT is arrived at by excluding known causes of secondary HT. Several theories have been proposed to explain the pathophysiology of primary HT in these patients and these are presented below.

Genetic Factors

Genetic factors play an important role in the pathophysiology of HT. Familial aggregation is observed commonly and both systolic and diastolic BPs were found to correlate significantly among siblings, the greatest concordance being between monozygotic twins. Interestingly, the highest parent-offspring correlation occurred between father and son but none was observed between father and daughters [15]. There are abundant data suggesting that either a major single gene effect, or more likely, several genes acting independently or in combination may control BP. This could happen by several mechanisms which may influence cation transport enhancement, salt sensitivity, catecholamine response to stress and the renin-angiotensin-aldosterone axis [16]. Several molecular genetic studies have identified mutations in genes that cause Mendelian forms of HT and hypotension in humans. These mutated genes typically impart large variations on BP, but of interest is the fact that in spite of the various physiologic systems that affect BP regulation, the mutated gene products in all cases act by altering net renal salt reabsorption. At least 8 monogenic forms of hypotensive and 9 of hypertensive syndromes have been identified in the past decade or so. Thus, inactivating mutations in various transporters and ion channels in the thick ascending limb of Henle’s loop, distal convoluted tubules and cortical collecting ducts result in Bartter’s, Gitelman’s and pseudohypoaldosteronism type 1 syndromes respectively, all conditions associated with renal salt wasting and a tendency for low BP. Monogenic forms of HT include Liddle’s syndrome (Epithelial Na channel, ENaC, mutations), pseudohypoaldosteronism type 2 or Gordon’s syndrome (WNK kinase 1 and 4 mutations), the syndrome of Apparent Mineralocorticoid Excess (AME), and Glucocorticoid Remediable Aldosteronism (GRA). All these rare syndromes are associated with renal salt retention and either potassium wasting as seen in Liddle’s syndrome, AME and GRA or potassium retention as in Gordon’s syndrome [17]. While no clear cut correlation exists between any of these mutated genes and essential HT, there is suggestive evidence that the ENaC and WNK kinase pathways appear to be plausible candidates. Recent studies from the Lifton laboratory at Yale reveal that heterozygous mutations in the Bartter’s genes, though rare, seem to be protective against the development of hypertension in adults [18].

The incidence, prevalence and severity of essential HT are significantly higher in black American adults compared to whites. Comparative data for children, though less convincing, have been shown by meta-analysis recently to be similar to the adult population. This is particularly observed with maximal dynamic exercise where systolic BP was consistently higher in black subjects. The same is true for salt sensitivity in blacks who show a higher BP rise with a high sodium diet and lower plasma renin activity than white subjects [19].
Predictors of Adult HT

Low Birth Weight

There seems to be an inverse correlation between birth weight and BP at different ages later in life. While this is no longer remains a controversial issue, possible mechanisms include structural changes in the renal blood vessels leading to impaired endothelial development, increased sensitivity to glucocorticoids, reduced nephron mass with subsequent hyperfiltration and glomerulosclerosis [20]. Nephron endowment is particularly sensitive to intrauterine growth restriction. If rapidsomatic growth occurs subsequently, the kidney may not be able to respond with an increase inheprenon number. The adaptive hypertrophy of existing nephronsrenders the kidney susceptible to hypertensive and sclerotic events (fig 2) [21, 22].

Systolic Blood Pressure in Childhood

There is a good correlation with systolic BP above the 90th percentile in children and later development of adult HT. Also, BP responses to exercise and mental stress are important predictors of BP elevation later in life [23]. Other predictors include family history of HT, ischemic heart disease and stroke. These are associated with high BP in young adults and adolescents. Body mass index (BMI) in childhood appears to be an important predictor of high BP in adults. Also, overweight individuals are more likely to have high LDL cholesterol, lower HDL cholesterol and higher insulin levels and greater propensity for type 2 diabetes and the metabolic syndrome.

Potassium and Sodium

Potassium may play an important role in BP regulation, probably through its propensity to induce natriuresis and suppression of renin production and release. Potassium intake has been shown to have an inverse relationship with both systolic and diastolic BP in children. Dietary potassium and the ratio of potassium to sodium may be more important than dietary sodium alone in its relationship to systolic BP. Studies have shown that increasing the potassium intake of hypertensive rats that were fed high-sodium diets lowered BP, reduced the incidence of stroke and stroke-related death, and prevented cardiac hypertrophy, mesenteric vascular damage, and renal injury [25, 26]. A recent systematic review and meta-analysis showed high quality evidence that increasing potassium intake reduces BP in both adults and children with HT and has no adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function in adults. Also there was moderate quality evidence that higher potassium intake was associated with a 24% lower risk of stroke suggesting that increased potassium intake is potentially beneficial to most people without impaired renal handling of potassium for the prevention and control of elevated BP and stroke [27]. As for the role of sodium in essential HT, the controversy abounds. While there is no dispute that excessive salt intake is associated with HT, only 40% of adults with HT appear to manifest salt sensitivity and this is more commonly seen in blacks, women and in older individuals. A meta-analysis of randomized controlled trials lasting at least 4 weeks concluded that reducing sodium intake by 50 mmol per day decreases systolic BP by an average of 4.0 mm Hg and diastolic BP by an average of 2.5 mm Hg in hypertensive patients. In normotensive subjects the systolic and diastolic BP fell very modestly by an average of 2.0 mm Hg and 1.0 mm Hg respectively [28].

Secondary Hypertension

As stated earlier, the probability of diagnosing a secondary cause of HT is directly related to the degree of BP elevation and inversely to the age of the child. The most common causes of HT seen in children of various age groups are listed in Table 1[29] and discussed below.
In newborn infants umbilical artery catheterization and related thromboembolization of the renal vessels is the most common identifiable cause of hypertension. This is followed by bronchopulmonary dysplasia (premature babies) and congenital anomalies of the kidney and urinary tract. Less common causes are renal vein thrombosis and coarctation of the aorta.

In the first year of life aortic coarctation is the most common cardiovascular cause of HT with a male to female ratio of 1.74. It is also diagnosed in one third of patients with Turner’s syndrome. Physical findings consist of diminished femoral pulses, a systolic pressure gradient between right arm and leg BP, and a systolic murmur heard over the left interscapular area. Renal parenchymal disease is another major cause of HT in this age group. Less common causes are renal vein thrombosis and coarctation of the aorta.

From 1-6 years of age, prenatal and neonatal conditions listed above that may have been missed in the first year of life may be recognized during this period. Both unilateral and bilateral reflux nephropathy may be associated with HT which may be severe. A past medical history of febrile urinary tract infections may be a key to the clinical diagnosis of chronic pyelonephritis, although as many as 30% show no evidence of vesico-ureteral reflux. Renal parenchymal disease has an important role in the etiology of HT in this age group. Both heredofamilial (genetic) and acquired diseases of the kidney encompass a variety of conditions associated with HT. Among the former, hereditary nephritis (Alport’s syndrome), an X-linked, but with occasional autosomal recessive or dominant transmission should be suspected in patients.
presenting with asymptomatic episodes of gross hematuria. In the juvenile form, patients may develop severe sensorineural deafness early in the course of the disease. Ocular abnormalities, including lenticonus and retinopathy are common. Patients with autosomal recessive polycystic kidney disease (ARPKD) who survive the perinatal period express variable disease phenotypes with systemic HT, renal insufficiency, and portal HT due to associated congenital hepatic fibrosis.

Nephronophthisis (NPHP) and medullary cystic kidney disease (MCKD) complex encompass two similar entities in their clinical and pathological presentation but expressing considerable genetic heterogeneity; nephronophthisis being a recessive disease while MCKD is inherited by a dominant gene. There are at least 13 genes for nephronophthisis (NPHP) and 2 genes for MCKD. For NPHP, the clinical presentation is that of progressive renal impairment typical of chronic tubulointerstitial without significant proteinuria but with varying degrees of polyuria metabolic acidosis (renal tubular acidosis). Association with other major organ involvement is common, including retinitis pigmentosa, skeletal defects and central nervous system abnormalities. Various acquired renal diseases also cause HT. Both, acute and chronic glomerular diseases are frequently associated with HT. These include post infectious glomerulonephritis, crescentic nephritis with or without pulmonary hemorrhage, Henoch–Schoenleinpurpura nephritis, IgA nephropathy and various vasculitic syndromes including lupus nephritis, polyarteritis nodosa, scleroderma and others. Nephrotic syndrome secondary to focal segmental glomerulosclerosis is frequently associated with HT. Hemolytic uremic syndrome, both in the acute and chronic form is a common cause of HT.

Hypertension may be secondary to extra-cellular fluid volume overload in acute oligoanuric renal failure. In chronic renal failure this may be due to renal release of pressor substances such as angiotensin 2, endothelin and others. Hypertension also occurs frequently following renal transplantation where the etiology is multifactorial and includes fluid overload, corticosteroids, calcineurin inhibitors, allograft rejection and renal artery stenosis. Several medications including eye and nose drops, exogenous steroids, cyclosporin and NSAIDS may cause drug induced HT. Other causes include infiltrative diseases, trauma, and renal tumors. Renovascular disease, mainly renal artery stenosis due to various types of fibromuscular dysplasia, although rare in absolute terms, is relatively a common cause of HT in this age group. Coarctation of the aorta is still diagnosed with relative frequency in this age group (see above). Endocrine diseases are infrequent causes of HT, but should be suspected if there is associated hypokalemia invoking syndromes of mineralocorticoid excess such as 11ß-hydroxylase and17α-hydroxylase deficiencies and much less frequently with primary aldosteronism. Adrenomedullary and sympathetic chain functional tumors such as pheochromocytoma and neuroblastoma are also considered as very rare causes of HT. Essential hypertension is extremely rare in this age bracket and basically remains a diagnosis of exclusion.

From 6-12 years the etiology of HT is similar to the previous age bracket, with renal parenchymal and renovascular diseases being the most common causes, but primary or essential HT comes third in frequency, ahead of coarctation of the aorta and endocrine causes.

From 12- 20 years of age, essential HT, which is being diagnosed with increased frequency in this age group, probably accounts for the etiology in most children with asymptomatic or symptomatic HT. This is particularly true for overweight children and those with a positive family history of HT. Iatrogenic causes of HT are also relatively common in this age group. In addition to the drugs mentioned earlier, the contraceptive pill plays a significant role in the etiology of HT of young females. Other causes of HT with decreasing frequency include renal parenchymal and renovascular diseases, endocrine causes and coarctation of the aorta.

**Diagnostic Evaluation**

In the first year of life, virtually all hypertension is secondary, and even in infants in whom no cause was found secondary disease must still be suspected. As stated previously, the likelihood of identifying a secondary cause of hypertension is directly related to the degree of BP elevation and inversely related to the age of the child. Also, given the low prevalence of secondary disease in the adolescent population with mild hypertension, only minimal studies are warranted.

**History**

A hypertension-oriented history should be elicited with emphasis on the following factors:

1. Symptoms referable to hypertension. Hypertension is often thought of as a silent disease because typically there have not been any classic symptoms. However, a recent study by Croix and Feig[28] found that 51% of untreated hypertensive children when surveyed reported 1-4 symptoms, and 14% reported more than four symptoms. Three most common symptoms include headache (42%), difficulty initiating sleep (27%), daytime tiredness (27%). These all improved with treatment.

2. Neonatal course: Birth weight, gestational age, history of umbilical lines
3. Growth pattern: Impaired growth might reflect an underlying chronic kidney disease
4. History of renal/urologic problems: hematuria, proteinuria, edema, urine infections
5. Use of medications such as decongestants, stimulants, NSAIDS, steroids...
6. Symptoms of endocrine etiology: flushing, sweating, tachycardia...
7. Family history of primary HT, genetic disorders known to be associated with secondary HT.

**Physical Examination**

Blood pressure should be measured routinely in children 3 years...
and older as well as in younger children with conditions known to be associated with HT such as cardiovascular, renal and endocrine related diseases. Initial BP should be recorded in both upper and lower extremities with the child seated (supine). Femoral and dorsalis pedis pulses should be palpated bilaterally. The child’s height and weight centiles and calculated BMI should be documented. The exam should focus on detailed findings that may provide clues to a specific diagnostic entity. With severe HT, look for evidence of hypertensive encephalopathy, Bell’s palsy, retinopathy and other neurologic deficits; cutaneous manifestations such as neurofibromas, café-au-lait spots, should arouse suspicion for neurofibromatosis and pheochromocytoma, Von Hippel-Lindau disease, tuberous sclerosis. Cushingoid features (moon facies, hirsutism, buffalo hump, truncal obesity, striae) and precocious puberty suggest adrenal or pituitary disorders. Other specific findings include thymomegaly, cutaneous lesions of systemic lupus erythematosus, Henoch–Schönlein purpura and other vasculitic syndromes. Additional findings may include pulmonary edema, congestive heart failure as signs of left ventricular dysfunction. Peripheral edema may point to kidney disease. One should not miss signs of pregnancy, features of Turner’s and Williams’ syndrome, enlarged kidneys and abdominal masses.

**Laboratory and Imaging**

Phase 1 - Screening: CBC, urinalysis, urine culture (if indicated), BUN, Creatinine, electrolytes, calcium, phosphorous, uric acid and lipid panel, EKG, echocardiogram, Doppler ultrasound of renal arteries.

Phase 2: Specific Tests: Renin profiling, renal scan with ACEI- to rule out renovascular HT, urine catecholamines to rule out pheochromocytoma, plasma and urinary steroids to rule out adrenocortical HT

Phase 3: Advanced Tests: CT Angiography for RVHT, Metaiodobenzguanidine (MIBG) scan of adrenals for pheochromocytoma, Caval sampling for catecholamines (as above), DMSA renal scan to rule out renal scars.

**Management**

**Non-pharmacologic Measures: Life Style Modifications**

Non-pharmacologic interventions are currently recommended as the initial approach to children and adolescents with mild hypertension with no evidence of target organ involvement. Generally, management should begin with smoking cessation, weight loss, aerobic exercise, and dietary modifications (DASH diet) with high potassium calcium and magnesium. Although demonstrated in some adults, the limitation of sodium intake and its positive impact on BP is less clear in children. Despite the lack of large scale trials demonstrating the effectiveness of such interventions, it is reasonable to recommend them given the benefits observed in the adult population.

**Pharmacologic Therapy**

Drug treatment for childhood hypertension should be started when it is associated with symptoms (see Diagnostic Evaluation). Other absolute indications include hypertensive target-organ damage (left ventricular hypertrophy, renal involvement, retinopathy and central nervous system disease), secondary hypertension, pre-existing diabetes types 1 and 2 and persistent hypertension despite non-pharmacological intervention. Relative indications for pharmacotherapy include the following: sustained or nocturnal hypertension on ambulatory monitoring, presence of other cardiovascular risk factors (smoking, elevated lipids), obesity related hypertension family history of hypertension.

The goal is to achieve a decrease in BP to below the 90th to 95th percentile and prevent long term sequelae of persistent hypertension. Most children with secondary hypertension require pharmacotherapy and frequently more than one medication. We usually start with a stepped-up approach using the lowest recommended dose and titrating it against the blood pressure response until the highest recommended dose is reached or side effects are observed. A second drug may be added at this point until normotension is attained. Patients with secondary hypertension may benefit from specific drugs acting on the altered physiology responsible for the hypertension. Thus, patients with high-renin hypertension, proteinuric renal diseases, renovascular HT and patients with diabetes would likely benefit more from ACE inhibitors or ARBs. The recommended doses for commonly used oral antihypertensive drugs in children and adolescents are shown in Table 2. The diagnosis and management algorithm for children with hypertension is shown in Figure 3.

**Summary**

Hypertension and obesity in children are increasing steadily worldwide. For accurate confirmation of the diagnosis of HT, ABPM is superior to casual clinic BP measurements. Once discovered, elevated BP should be appropriately investigated with the laboratory and radiologic evaluation tailored to the age of the child and the severity of the BP elevation. Recent data suggest that the treatment of childhood hypertension may reduce cardiovascular and renal morbidity risk in adulthood. Therefore, once confirmed, hypertension in children should be treated expeditiously.
Figure 3: Recommended algorithm for the work up and management of hypertension in children and adolescents. Reproduced from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, Pediatrics 2004;114:555-576.
| Drug          | Starting dose mg/kg/day | Interval   | Maximum daily dose               |
|--------------|-------------------------|------------|----------------------------------|
| **ACEI**     |                         |            |                                  |
| Captopril    | 0.6-6.0                 | BID-QID    | 6 mg/kg/day, 450mg/day           |
| Enalapril    | 0.08-0.6                | QD-BID     | 40 mg/day                        |
| Lisinopril   | 0.07-0.6                | QD         | 40 mg/day                        |
| **ARB**      |                         |            |                                  |
| Candesartan  | 0.05-0.4                | QD         | 32 mg/day                        |
| Losartan     | 0.7-1.4                 | QD         | 100 mg/day                       |
| Valsartan    | 1.3-2.7                 | QD         | 80-160 mg/day                    |
| **Alpha/Beta Blockers** |       |            |                                  |
| Labetalol    | 1.0-3.0                 | BID        | 1200 mg/day                      |
| Carvediol    | 0.1-0.5                 | BID        | 25 mg/day                        |
| **Beta Blockers** |                  |            |                                  |
| Atenolol     | 0.5-2.0                 | QD-BID     | 100mg/day                        |
| Metoprolol   | 1-2                     | BID        | 200mg/day                        |
| Propanolol   | 0.5-4.0                 | BID-TID    | 640 mg/day                       |
| **Calcium Channel Blockers** |          |            |                                  |
| Amlodipine   | 0.05-0.6                | QD-BID     | 10 mg/day                        |
| Felodipine   | 2.5/day                 | QD         | 10 mg/day                        |
| Isradipine   | 0.05-0.15               | TID-QID    | 20 mg/day                        |
| **Central Agonist** |                 |            |                                  |
| Clonidine    | 10-30 mcg               | BID-TID    | 2.4 mg/day                       |
| **Diuretics** |                        |            |                                  |
| Spironolactone | 1.0-3.3                | QD-BID     | 100mg/day                        |
| Chlorthalidone| 0.3-2.0                 | QD         | 50 mg/day                        |
| Furosemide   | 0.5-6.0                 | QD-QID     | 600 mg/day                       |
| HCTZ         | 0.5-3.0                 | QD         | 50 mg/day                        |
| **Peripheral Alpha-1 Blocker** |         |            |                                  |
| Prazosin     | 0.05-0.1                | BID-TID    | 20 mg/day                        |
| **Vasodilators** |                    |            |                                  |
| Hydralazine  | 0.75-7.5                | TID-QID    | 200 mg/day                       |
| Minoxidil    | 0.1-2.2                 | BID-TID    | 50 mg/day                        |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide
References

1. Nwankwo T, Yoon SS, Burt F and Gu Q (2013) Hypertension among adults in the United States: National Health and Nutrition Examination Survey(2011–2012).

2. Cheng X, Wang Y (2008) Tracking blood pressure from childhood to adulthood: a systematic meta-regression analysis. Circulation 117:3171-80.

3. Sun SS, Grave GD, Siervogel RM (2007) Systolic blood pressure in childhood predicts hypertension and metabolic syndrome later in life. Pediatrics 119:237-46.

4. Falkner B (2010) Hypertension in children and adolescents: epidemiology and natural history. Pediatr Nephrol 25:1219-24.

5. McNiece KL, Poffenbarger TS, Turner JL (2007) Prevalence of hypertension and prehypertension among adolescents. J Pediatr 150:640-644.

6. Sorof JM, Lai D, Turner J, Poffenbarger TS, Portman RJ, et al. (2004) Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics 113:475-82.

7. Chobanian AV, Bakris GL, Black HR (2003) Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 289: 2560-72.

8. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. (2004) The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics 114:555-76.

9. Lauer RM, Clarke WR (1989) Childhood risk factors for high adult blood pressure: The Muscatine study. Pediatrics 84: 633-41.

10. Flynn, JF In: Elzouki AY Ed (2012) Textbook of Clinical Pediatrics vol 4. 2nd ed Heidelberg Springer. 2724-2742.

11. Raj M, Krishnakumar R (2013) Hypertension in children and adolescents: epidemiology and pathogenesis. Indian J Pediatr 80:571-576.

12. Hansen ML, Gunn PW, Kaehler DC (2007) Underdiagnosis of hypertension in children and adolescents. JAMA 298: 874-9.

13. Sorof J, Daniels S (2002) Obesity hypertension in children. Hypertension. 40:441-447.

14. Couch SC, Daniels S (2005) Diet and blood pressure in children. Current Opinion in Pediatrics 17: 648-652.

15. Patterson TL, Kaplan RM, Sallis JF (1987) Aggregation of blood pressure in Anglo-American and Mexican-American families. Prev Med 16:616-625.

16. Schieken RM (1993) Genetic factors that predispose the child to develop hypertension. Pediatr Clin North Am 40: 1-11.

17. Lifton RP, Gharavi AG, Geller DS (2001) Molecular mechanisms of human hypertension. Cell 104: 545-56.

18. Ji W, Foo JN, O’Roak BJ (2008) Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 40: 592-598.

19. Alpert BS, Fox ME (1993) Racial aspects of blood pressure in children and adolescents. Pediatr Clin North Am. 40: 13-22.

20. Davies AA, Smith GD, May MT, Ben-Shlomo Y (2006) Association between birth weight and blood pressure is robust, amplifies with age, and may be underestimated. Hypertension 48: 431-6.

21. Ingelfinger J R, Schnaper H W (2005) Renal endowment: Developmental origins of adult disease. JASN 16:2533-2536.

22. Bagby SP (2004) Obesity-initiated metabolic syndrome and the kidney: A recipe for chronic kidney disease? JASN 15:2775-91.

23. Lauer RM, Clarke WR, Mahoney LT, Witt J (1993) Childhood predictors for high adult blood pressure. Pediatr Clin North Am 40: 23-40.

24. Bogaert YE, Linas S (2009) The role of obesity in the pathogenesis of hypertension. Nat Clin Pract Nephrol. 5:101-11.

25. Adrogué, HJ, Madias NE (2007) Sodium and potassium in the pathogenesis of hypertension. N Engl J Med 356:1966-78.

26. Liu DT, Wang MX, Kincaid-Smith P, Whitworth JA (1994) The effects of dietary potassium on vascular and glomerular lesions in hypertensive rats. Clin Exp Hypertens 16:391-414.

27. Aburto NJ, Hanson S, Gutierrez H (2013) Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 346: f1378.

28. He FJ, MacGregor GA (2003) How far should salt intake be reduced?. Hypertension 42:1093-9.

29. Sanjad SA (2010) Etiology of hypertension in children and adolescents. J Med Liban 58:142-5.

30. Croix B, Feig D (2006) Childhood hypertension is not a silent disease. Pediatr Nephrol 21:527-32.