Review Article

Essential hypertension in adolescents and children: Recent advances in causative mechanisms

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ABSTRACT

Essential hypertension is the most common form of hypertension in adults, and it is recognized more often in adolescents than in younger children. It is well known that the probability of a diagnosis of essential hypertension increases with age from birth onward. The initiation of high blood pressure burden starts in childhood and continues through adolescence to persist in the remaining phases of life. The genesis of essential hypertension is likely to be multifactorial. Obesity, insulin resistance, activation of sympathetic nervous system, sodium homeostasis, renin-angiotensin system, vascular smooth muscle structure and reactivity, serum uric acid levels, genetic factors and fetal programming have been implicated in this disorder. In addition, erythrocyte sodium transport, the free calcium concentration in platelets and leukocytes, urine kallikrein excretion, and sympathetic nervous system receptors have also been investigated as other possible mechanisms. Obesity in children appears to be the lead contributor of essential hypertension prevalence in children and adolescents. Suggested mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of renin-angiotensin-aldosterone, and altered vascular function. The etiopathogenesis of essential hypertension in children and adolescents appears to closely resemble that of adults. The minor variations seen could probably be due to the evolving nature of this condition. Many of the established mechanisms that are confirmed in adult population need to be replicated in the pediatric age group by means of definitive research for a better understanding of this condition in future.

Key words: Adolescents, children, essential hypertension, etiology, pathogenesis

INTRODUCTION

Essential hypertension is the most common form of hypertension in adults and it is recognized more often in adolescents than in younger children.[1] Hypertension is a major contributor to the global burden of disease. Worldwide, 7.6 million premature deaths were attributed to high blood pressure in 2001.[2] Roughly half of stroke and ischemic heart disease events worldwide were attributable to high blood pressure during the same period.[2] Suboptimal blood pressure was reported to account for 10% of global health care expenditure in 2001 for population aged 30 years and more.[3] The global public health significance of high blood pressure in childhood and adolescence is based on observations that confirm a strong tracking of blood pressure levels from childhood to adulthood.[4] It is well known that the probability of a diagnosis of essential hypertension increases with age from birth onward.[1] Children and young adolescents with blood pressure greater than the 90th percentile for age have roughly threefold greater likelihood of becoming adults with hypertension compared to their peers with blood pressure at the 50th percentile.[1] These findings clearly suggest that the initiation of high blood pressure burden starts in childhood and continues through adolescence to persist

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.86981

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in the remaining phases of life. The current review is an attempt to present recent research in basic etiopathogenesis of essential hypertension in children and adolescents.

Etiopathogenesis of Essential Hypertension

The genesis of essential hypertension is likely to be multifactorial. Obesity, insulin resistance, activation of sympathetic nervous system, sodium homeostasis, renin-angiotensin system (RAS), vascular smooth muscle structure and reactivity, serum uric acid levels, genetic factors and fetal programming have been implicated in this disorder.[1,5-8] In addition, erythrocyte sodium transport, the free calcium concentration in platelets and leukocytes, urine kallikrein excretion, and sympathetic nervous system receptors have also been investigated.[1]

Obesity and high blood pressure

Obesity in children is well known to be associated with hypertension. Data from a recent study covering 25,000 school children in the age group of 5–16 years reported increased prevalence of prehypertension and hypertension among overweight and obese children when compared to their non-overweight counterparts.[9] Hypertension (first instance) was seen in 10.10% of normal weight, 17.34% of overweight and 18.32% of obese children in this study. The corresponding figures for systolic hypertension were 5.38%, 12.31% and 14.66%, respectively. The same for diastolic hypertension were 6.45%, 8.86% and 8.90%, respectively.[9] Suggested mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of renin-angiotensin-aldosterone system (RAAS), and altered vascular function.[10] Probable reasons for activation of the sympathetic nervous system in obesity include hyperinsulinemia and/or insulin resistance; leptin, adiponectin or other adipokines; renin-angiotensin; and lifestyle factors.[10] Obesity-related hypertension is associated with renal sodium retention and impaired pressure natriuresis.[11] Circulating adiponectin levels are decreased in obesity-induced insulin resistance, and some studies suggest that adiponectin is protective against hypertension through an endothelial-dependent mechanism.[12,13]

Sodium and high blood pressure

Sodium and sodium-related mechanisms have been investigated in detail for their role in essential hypertension. These include dietary sodium load, salt sensitivity and an impaired ability for urinary excretion of a sodium load. Evidence from epidemiological, clinical and experimental studies confirms a strong relationship between dietary salt, renal salt handling and blood pressure.[14] Blood pressure response to changes in salt intake, namely, salt sensitivity, exhibits marked heterogeneity on an individual basis.[15] Salt sensitivity is defined as an augmentation of mean arterial pressure on 24-hour ambulatory blood pressure monitoring during increased salt intake.[16,17] Weinberger *et al.* reported that 51% of hypertensives and 26% of normotensives were sodium sensitive.[18] The distribution of salt sensitivity and resistance in normal and hypertensive subjects is bell shaped, and in both the proportion of individuals who become salt sensitive increases with age.[14] Familial patterns to acute and chronic salt challenges have been reported, but the genetic basis of salt sensitivity remains poorly known.[19,20] In one study done on 44 families of identical twin children who participated in a sodium restriction protocol, mother–offspring resemblance in blood pressure change with sodium restriction was significant both for systolic and diastolic blood pressure.[21] Sibling–sibling and twin–twin resemblance was also highly significant in this study. Body sodium and blood pressure regulation is achieved through the interaction of several mechanisms, starting from sodium handling in kidney tubular cells, moving to the myogenic tone at vascular level.[22] Physical, nervous, and hormonal factors modulate the ability of tubular cells to transport sodium according to the body's needs.[23] A defect in sodium excretion is also seen as a contributor to essential hypertension. Normally, sodium excretion increases when there is an acute increase in blood pressure. In persons with hypertension, however, the blood pressure required to excrete a given sodium load is higher than that in persons without hypertension.[24] This may be related to a congenital reduction in the number of nephrons, limiting the filtration of sodium.[25] Genetic alterations in the expression or regulation of vasoactive mediators or transport molecules involved in sodium excretion may also contribute to the development of hypertension.[26]

Renin-angiotensin system and high blood pressure

The RAS is believed to play a major role in regulating blood pressure and body fluid volumes, as evidenced by the effectiveness of various RAS blockers in reducing arterial pressure in normotensive and hypertensive subjects.[27] The physiologic functions of RAS are exerted mainly by angiotensin II, which participates in both short-term and long-term blood pressure regulation. Angiotensin II is a powerful vasoconstrictor and contributes to the maintenance of blood pressure in conditions associated with acute volume depletion or circulatory depression.[27] The long-term effects of angiotensin II on blood pressure are closely linked with volume homeostasis through direct and indirect effects on renal excretory function.[28] Two comparative studies done on offspring of hypertensive and non-hypertensive parents failed to document any major

differences in RAS activity between the two groups in childhood in spite of them showing differences in blood pressure levels.[29,30] The RAAS was investigated in offspring of essential hypertensives and in offspring of normotensive parents, both aged 5–34 years.[29] Offspring of essential hypertensives showed higher systolic and diastolic blood pressure values than those of normotensive parents. With the exception of significant, lower mean supine plasma aldosterone values in children of hypertensive parents, no major differences between the two groups were seen in supine and stimulated plasma renin activity, and stimulated aldosterone.[29] A recent cross-sectional study performed in 211 healthy normotensive children aged 4–16 years with hypertensive parents and normotensive parents replicated similar findings. Although the two groups of children were normotensive, the group of children with hypertensive parents had a higher systolic blood pressure (SBP) index than those with normotensive parents. In spite of this difference, there were no significant differences in serum aldosterone, plasma renin activity or aldosterone/renin ratio.[30] These two studies suggest that currently there is lack of evidence confirming an active role for RAS activation in pediatric essential hypertension.

Insulin resistance and blood pressure

Insulin resistance plays a major role in the pathogenesis and clinical course of patients with essential hypertension.[31] Approximately 50% of adult patients with essential hypertension, both treated and untreated, appear to be insulin resistant.[32] Insulin resistance and hyperinsulinemia appear to develop in obese children at an early age.[33,34] Insulin can be a determinant of blood pressure in children similar to that in adults.[35] The association between fasting insulin and blood pressure appears to be independent of adiposity.[35] The relationship between insulin sensitivity and systolic blood pressure is evident early in life.[36] In a study on 101 children, Cruz *et al.* reported that fasting insulin and the acute insulin response were positively related to systolic blood pressure but not to diastolic blood pressure, and insulin sensitivity was negatively related to systolic blood pressure but not to diastolic blood pressure. Insulin sensitivity was negatively associated with systolic and diastolic blood pressure after adjustment for body composition. This study also suggests that low insulin sensitivity contributes independently to higher blood pressure in children.[36] The probable reasons by which insulin resistance and/or hyperinsulinemia may increase the blood pressure include an anti-natriuretic effect of insulin, increased sympathetic nervous system activity, augmented responses to endogenous vasoconstrictors, altered vascular membrane cation transport, impaired endothelium-dependent vasodilatation and stimulation of vascular smooth muscle growth by insulin.[10] The compensatory hyperinsulinemia resulting from insulin resistance results in a paradoxical situation of benefit on one side and harm on the other. This is probably due to the fact that all tissues in the body are not equally resistant to the actions of insulin in the so-called state of insulin resistance.[31] The kidney in insulin resistance remains to be sensitive to insulin, thereby retaining the ability of insulin to enhance renal sodium reabsorption. This probably explains higher salt sensitivity and resultant salt and water retention in individuals with insulin resistance and/or hyperinsulinemia.[37] The sympathetic nervous system also remains to be normally sensitive to insulin, favoring vasoconstriction and sodium retention as a response to hyperinsulinemia resulting from insulin resistance.[38,39] Thus, the pancreatic b-cell response with an intention to maintain normal glucose homeostasis in an individual with adipose tissue and muscle insulin resistance results in augmenting the risk of developing essential hypertension.[31]

Sympathetic nervous system activation and hypertension

Studies in the past have suggested that sympathetic activation probably has a dynamic role in the development of the hypertensive state.[5] Sympathetic activation represents a major link between the hemodymanic (increased peripheral vascular resistance, decreased arterial distensibility, impaired organ perfusion, etc.) and the metabolic (insulin resistance, dyslipidemia, etc.) abnormalities frequently associated with hypertension.[5] In subjects with borderline or very mild hypertension, sympathetic nerve traffic is increased, indicating that central sympathetic outflow is already activated.[40,41] The level of the sympathetic neural activation appears to parallel the severity of the blood pressure elevation.[42] Plasma norepinephrine values are already elevated in young hypertensive subjects with mild blood pressure increase.[43] Resting tachycardia probably resulting from increased levels of norepinephrine is consistently seen in these young patients.[43] The increased sympathetic activity is probably due to a derangement in the sympatho-inhibition exerted by reflexogenic areas (such as the arterial baroreceptors, the cardiopulmonary receptors or the chemoreceptors) that restrain adrenergic outflow in normal individuals.[44] Metabolic alterations associated with hypertension, such as the hyperinsulinemic state and the related insulin resistance, may be the triggering factors for this stage.[45] An increase in sympathetic drive can also result in blood pressure elevation via an increase in renal sodium reabsorption.[44] High heart rate is a known predictor for the development of essential hypertension.[46] Whether heart rate itself is a risk factor for development of hypertension or is just a marker for sympathetic overactivation is still unclear. Increases in blood pressure variations as well as levels in childhood and adolescence are also predictive of adult hypertension.[47] Considering the role of sympathetic

nervous system in heart rate and blood pressure variability, the same also provides support for the role of sympathetic nervous system in the evolution of essential hypertension in childhood and adolescence.

Vascular smooth muscle function and high blood pressure

Blood vessels are under constant mechanical loading from blood pressure and flow which cause endothelial shear stress as well as circumferential wall stress.[48] In addition to the morphological changes of endothelium and blood vessel wall, the same mechanical forces also trigger biochemical and biological events.[48] The normal endothelium responds to hemodynamic forces and biochemical signals from the blood by synthesizing and releasing vasoactive substances.[48] Endothelial-dependent flow-mediated vasodilation is predominantly modulated by endothelium-derived nitric oxide, which stimulates soluble guanylyl cyclase activity in vascular smooth muscle cells.[49] Studies have shown that hypertension is associated with impaired flow-mediated arterial dilation, suggesting that endothelial dysfunction is probably playing an important role in the evolution of hypertension.[50,51] Endothelium-mediated vasodilation is impaired in patients with essential hypertension.[50] Patients with essential hypertension have increased vascular endothelin activity, which may be related to their increased vascular tone.[52] Endothelin is the most potent vasoconstrictor substance produced by the cardiovascular system.[52] Children and adolescents with hypertension have higher plasma concentration of endothelin-1 (ET-1) than healthy subjects and the same correlates with systolic blood pressure levels.[53] Endothelial dysfunction also contributes significantly to increased arterial stiffness in patients with hypertension.[51] Similar findings were reported from the pediatric population as well.[54,55] In a study involving 247 healthy subjects aged 10–20 years, Jourdan *et al.* demonstrated that systolic blood pressure is strongly associated with intima media thickness and vascular elasticity.[54] Functional and anatomical changes in elastic and muscular arteries were observed in newly diagnosed children with essential hypertension.[55] Hypertensive children had greater values of both carotid and femoral intima media thickness than controls. The distensibility and elasticity of the common carotid artery were significantly decreased in these hypertensive children, while arterial compliance was significantly greater than those in controls.[55]

Serum uric acid levels and high blood pressure

Hyperuricemia has been demonstrated to predict and be an independent risk factor for hypertension in adults.[56,57] Studies done in the pediatric population also demonstrated a significant correlation between elevated uric acid levels and blood pressure.[6,58] In one case–control study, uric acid levels were directly correlated with systolic and diastolic blood pressure in controls and in subjects with primary hypertension and were independent of renal function. Serum uric acid concentrations >5.5 mg/dL were found in 89% of subjects with primary hypertension, in 30% with secondary hypertension, in 0% with white-coat hypertension, and in 0% of controls.[58] The Bogalusa heart study concluded that childhood uric acid was significantly correlated with childhood and adult blood pressure, both systolic and diastolic.[6] Childhood uric acid levels and change in levels of uric acid were significant predictors of adult diastolic blood pressure.[6] Change in uric acid was a significant predictor of adult systolic blood pressure.[6] Uric acid can enter the vascular smooth muscle cells and stimulate a number of factors which are known to induce vascular smooth muscle proliferation and preglomerular arteriolopathy.[6,59,60] These changes produce salt sensitivity which remains persistent irrespective of future uric acid levels.[61] This form of persistent salt sensitivity is thought to be initiated by renal ischemia that in turn results in activation of the renal RAS, renal vasoconstriction, and increased sodium reabsorption.[62,63] Whether higher level of uric acid is a cause or a result of high blood pressure level in childhood and adolescence remains to be confirmed by definitive research.

Role of genes in essential hypertension

An estimated 30–60% of the variation in blood pressure between individuals, after adjustment for age and sex, is attributed to the effect of genetic factors.[7] A child with a history of hypertension in both parents, and who has a sibling with hypertension, has a 40–60% chance of developing hypertension as an adult.[64] If the sibling is a monozygotic twin, the risk of the same increases to 80%.[64] The genetic susceptibility to develop primary hypertension results from the effects of multiple genes and is modulated by multiple environmental determinants.[65] Using linkage studies and positional cloning in humans, a dozen genes responsible for monogenic forms of hypertension and hypotension or associated to essential hypertension have been identified.[66] All of these genes are either mediating or involved in the regulation of renal sodium transport.[67] These mutations alter the blood pressure through a common pathway, changing salt and water re-absorption in the kidney.[67] Genes encoding components of the RAAS, and angiotensinogen and angiotensin converting enzyme (ACE) polymorphisms may be related to hypertension .[7] The same may also be related to blood pressure sensitivity in response to dietary salt intake.[7] Normal functioning of endothelial ion channels is important in the control of vascular tone. Dysfunction of these ion channels could contribute to alterations in blood pressure.[68] Studies indicate that genetic defects in sodium transport across

cell membranes may be important in the development of primary hypertension in humans.[66,68] Genetically mediated alterations in the regulation or expression of renal ion channels and transporters may also be important in the genesis of hypertension.[65] Variations and mutations in other genes, such as α-adducin, atrial natriuretic factor, the insulin receptor, β2-adrenergic receptor, calcitonin gene-related peptide, angiotensinase C, renin-binding protein, endothelin-1 precursor, and G-protein b3-subunit, have also been reported to be associated with the development of essential hypertension.[7,69-72]

Fetal programming of blood pressure

Barker *et al.* hypothesized that influences during fetal life that slow fetal growth could program or permanently alter the body's structure and physiology involving major systems of the body and result in an adverse health profile in later life.[73] The majority of the studies in children, adolescents and adults included in a recent, extensive review on this topic reported that blood pressure fell with increasing birth weight, the size of the effect being approximately 2 mm Hg/kg.[74] Skeletal and non-skeletal postnatal catch-up growth were positively associated with blood pressure, with the highest blood pressures occurring in individuals of low birth weight but high rates of growth subsequently.[74] The underlying mechanisms that lead to these phenomena are still unclear and widely debated. When nutritional deficiency occurs in utero at a critical period of development, the resulting adaptive changes may be permanent and may lead to long-term changes in structure and function.[75] Birth weight is also associated with salt sensitivity of blood pressure, and this may play a role in the maintenance of elevated blood pressure in individuals with a low birth weight.[76,77] Simonetti *et al.* reported that renal mass is reduced in children born with low birth weight and depends on the degree of in utero growth retardation, which then determines lower glomerular filtration rate, increased salt sensitivity, and elevated blood pressure.[77] The fetal programming hypothesis of hypertension needs more definitive research to support itself.

Conclusion

The etiopathogenesis of essential hypertension in children and adolescents appears to closely resemble that of adults. The minor variations seen could probably be due to the evolving nature of this condition. More research efforts in pediatric population are needed to bring clarity to the role of many of the proposed mechanisms that are well established in adult population.

References

1. Bernstein D. Systemic Hypertension. In: Kliegman RM, Stanton BF, Geme JS, Schor N, Behrman RE, editors. Nelson's Textbook of Pediatrics. 19th ed. Philadelphia: Mosby Elsevier; 2010. p. 1988-95.
2. Lawes CM, Vander Hoorn S, Rodgers A; International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet 2008;371:1513-8.
3. Gaziano TA, Bitton A, Anand S, Weinstein MC; International Society of Hypertension. The global cost of nonoptimal blood pressure. J Hypertens 2009;27:1472-7.
4. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic review and meta-regression analysis. Circulation 2008;117:3171-80.
5. Grassi G. Sympathetic neural activity in hypertension and related diseases. Am J Hypertens 2010;23:1052-60.
6. Alper AB Jr, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. Hypertension 2005;45:34-8.
7. Singh M, Mensah GA, Bakris G. Pathogenesis and clinical physiology of hypertension. Cardiol Clin 2010;28:545-59.
8. Nuyt AM, Alexander BT. Developmental programming and hypertension. Curr Opin Nephrol Hypertens 2009;18:144-52.
9. Raj M, Sundaram KR, Paul M, Deepa AS, Kumar RK. Obesity in Indian children: Time trends and relationship with hypertension. Natl Med J India 2007;20:288-93.
10. Kotchen TA. Obesity-related hypertension: Epidemiology, pathophysiology, and clinical management. Am J Hypertens 2010;23:1170-8.
11. Hall JE. The kidney, hypertension, and obesity. Hypertension 2003;41:625-33.
12. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. J Clin Endocrinol Metab 2008;93(11 Suppl 1):S64-73.
13. Yiannikouris F, Gupte M, Putnam K, Cassis L. Adipokines and blood pressure control. Curr Opin Nephrol Hypertens 2010;19:195-200.
14. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 2005;85:679-715.
15. Haddy FJ. Role of dietary salt in hypertension. Life Sci 2006;79: 1585-92.
16. Sharma AM. Salt sensitivity as a phenotype for genetic studies of human hypertension. Nephrol Dial Transplant 1996;11:927-9.
17. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension 1996;27:481-90.
18. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 1986;8:II127-34.
19. Beeks E, Kessels AG, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: A systematic review. J Hypertens 2004;22:1243-9.
20. Luft FC. Molecular genetics of salt-sensitivity and hypertension. Drug Metab Dispos 2001;29:500-4.
21. Miller JZ, Weinberger MH, Christian JC, Daugherty SA. Familial resemblance in the blood pressure response to sodium restriction. Am J Epidemiol 1987;126:822-30.
22. Hill MA, Meininger GA, Davis MJ, Laher I. Therapeutic potential of pharmacologically targeting arteriolar myogenic tone. Trends Pharmacol Sci 2009;30:363-74.
23. Guyton AC, Langston JB, Navar G. Theory for renal autoregulation by feedback at the juxtaglomerular apparatus. Circ Res 1964;15 Suppl:187-97.
24. Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 1972;52:584-94.

25. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1988;1:335-47.
26. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996;272:676-80.
27. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: The overriding dominance of the kidney. J Am Soc Nephrol 1999;10 Suppl 12:S258-65.
28. Hall JE, Guyton AC, Brands MW. Control of sodium excretion and arterial pressure by intrarenal mechanisms and the renin-angiotensin system. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, Diagnosis and Management. 2nd ed. New York: Raven Press; 1995. p. 1451-75.
29. Studer A, Lüscher T, Greminger P, Epstein FH, Grimm J, Leumann EP, Tenschert W, Siegenthaler W, Vetter W. [Blood pressure, renin angiotensin aldosterone system and other cardiovascular risk factors in children of essential hypertensives (author's transl)]. Klin Wochenschr 1982;60:275-84.
30. Martinez-Aguayo A, Aglony M, Campino C, Garcia H, Bancalari R, Bolte L, *et al*. Aldosterone, plasma Renin activity, and aldosterone/renin ratio in a normotensive healthy pediatric population. Hypertension 2010;56:391-6.
31. Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: Similarities and differences. J Clin Hypertens (Greenwich) 2011;13:238-43.
32. Lima NK, Abbasi F, Lamendola C, Reaven GM. Prevalence of insulin resistance and related risk factors for cardiovascular disease in patients with essential hypertension. Am J Hypertens 2009;22:106-11.
33. Gower BA, Nagy TR, Goran MI. Visceral fat, insulin sensitivity, and lipids in prepubertal children. Diabetes 1999;48:1515-21.
34. Arslanian S, Suprasongsin C. Differences in the invivo insulin secretion and sensitivity of healthy black versus white adolescents. J Pediatr 1996;129:440-3.
35. Jiang X, Srinivasan SR, Bao W, Berenson GS. Association of fasting insulin with longitudinal changes in blood pressure in children and adolescents. The Bogalusa Heart Study. Am J Hypertens 1993;6:564-9.
36. Cruz ML, Huang TT, Johnson MS, Gower BA, Goran MI. Insulin sensitivity and blood pressure in black and white children. Hypertension 2002;40:18-22.
37. Facchini FS, DoNascimento C, Reaven GM, Yip JW, Ni XP, Humphreys MH. Blood pressure, sodium intake, insulin resistance, and urinary nitrate excretion. Hypertension 1999;33:1008-12.
38. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities -the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996;334:374-81.
39. Reaven GM. The Kidney: An unwilling accomplice in syndrome X. Am J Kidney Dis 1997;30:928-31.
40. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. Hypertension 1989;14:177-83.
41. Floras JS, Hara K. Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. J Hypertens 1993;11:647-55.
42. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 1998;31:68-72.
43. Julius S, Krause L, Schork NJ, Mejia AD, Jones KA, van de Ven C, *et al*. Hyperkinetic borderline hypertension in Tecumseh, Michigan. J Hypertens 1991;9:77-84.
44. Grassi G, Mancia G. Hyperadrenergic and labile hypertension. In: Lip GH, Hall J, editors. Comprehensive hypertension. Philadelphia: Mosby Elsevier; 2007. p. 719-26
45. Grassi G, Quarti-Trevano F, Dell'oro R, Mancia G. Essential hypertension and the sympathetic nervous system. Neurol Sci 2008;29 Suppl 1:S33-6.
46. Tjugen TB, Flaa A, Kjeldsen SE. High heart rate as predictor of essential hypertension: The hyperkinetic state, evidence of prediction of hypertension, and hemodynamic transition to full hypertension. Prog Cardiovasc Dis 2009;52:20-5.
47. Chen W, Srinivasan SR, Ruan L, Mei H, Berenson GS. Adult hypertension is associated with blood pressure variability in childhood in blacks and whites: The bogalusa heart study. Am J Hypertens 2011;24:77-82.
48. Lu D, Kassab GS. Role of shear stress and stretch in vascular mechanobiology. J R Soc Interface 2011;8:1379-85.
49. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, *et al*. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries *in vivo*. Circulation 1995;91:1314-9.
50. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323:22-7.
51. Wallace SM, Yasmin, McEniery CM, Mäki-Petäjä KM, Booth AD, Cockcroft JR, *et al*. Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. Hypertension 2007;50:228-33.
52. Cardillo C, Kilcoyne CM, Waclawiw M, Cannon RO 3rd, Panza JA. Role of endothelin in the increased vascular tone of patients with essential hypertension. Hypertension 1999;33:753-8.
53. Głowińska B, Urban M, Hryniewicz A, Peczyńska J, Florys B, Al-Hwish M. Endothelin-1 plasma concentration in children and adolescents with atherogenic risk factors. Kardiol Pol 2004;61:329-38.
54. Jourdan C, Wühl E, Litwin M, Fahr K, Trelewicz J, Jobs K, *et al*. Normative values for intima-media thickness and distensibility of large arteries in healthy adolescents. J Hypertens 2005;23:1707-15.
55. Litwin M, Trelewicz J, Wawer Z, Antoniewicz J, Wierzbicka A, Rajszys P, *et al*. Intima-media thickness and arterial elasticity in hypertensive children: Controlled study. Pediatr Nephrol 2004;19:767-74.
56. Selby JV, Friedman GD, Quesenberry CP Jr. Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol 1990;131:1017-27.
57. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, *et al*. Serum uric acid and hypertension: The Olivetti heart study. J Hum Hypertens 1994;8:677-81.
58. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension 2003;42:247-52.
59. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, *et al*. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991-7.
60. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem 1991;266:8604-8.
61. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: An indicator of renal vascular involvement. Ann Intern Med 1980;93:817-21.
62. Franco M, Tapia E, Santamaría J, Zafra I, García-Torres R, Gordon KL, *et al*. Renal cortical vasoconstriction contributes to development of salt-sensitive hypertension after angiotensin II exposure. J Am Soc Nephrol 2001;12:2263-71.
63. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Engl J Med 2002;346:913-23.
64. Slocks P. A biometric investigation of twins and their brothers and sisters. Ann Eugen 1930;4:49e62.

65. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001;104:545-56.
66. Meneton PG, Warnock D. Involvement of renal apical Na transport systems in the control of blood pressure. Am J Kidney Dis 2001;37(1 Suppl 2):S39-47.
67. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996;272:676-80.
68. Baker EH. Ion channels and the control of blood pressure. Br J Clin Pharmacol 2000;49:185-98.
69. Luft FC. Geneticism of essential hypertension. Hypertension 2004;43:1155-9.
70. Barlassina C, Lanzani C, Manunta P, Bianchi G. Genetics of essential hypertension: From families to genes. J Am Soc Nephrol 2002;13 Suppl 3:S155-64.
71. Luft FC. Molecular genetics of human hypertension. J Hypertens 1998;16:1871-8.
72. Williams RR, Hunt SC, Hopkins PN, Hasstedt SJ, Wu LL, Lalouel JM. Tabulations and expectations regarding the genetics of human hypertension. Kidney Int Suppl 1994;44:S57-64.
73. Barker DJ. In utero programming of chronic disease. Clin Sci (Lond) 1998;95:115-28.
74. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. J Hypertens 2000;18:815-31.
75. Alexander BT. Fetal programming of hypertension. Am J Physiol Regul Integr Comp Physiol 2006;290:R1-10.
76. de Boer MP, Ijzerman RG, de Jongh RT, Eringa EC, Stehouwer CD, Smulders YM, *et al*. Birth weight relates to salt sensitivity of blood pressure in healthy adults. Hypertension 2008;51:928-32.
77. Simonetti GD, Raio L, Surbek D, Nelle M, Frey FJ, Mohaupt MG. Salt sensitivity of children with low birth weight. Hypertension 2008;52:625-30.

Cite this article as: Raj M. Essential hypertension in adolescents and children: Recent advances in causative mechanisms. Indian J Endocr Metab 2011;15:367-73.

Source of Support: Nil, **Conflict of Interest:** None declared.