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Primary Pediatric Hypertension: Current Understanding and Emerging Concepts

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Abstract

The rising prevalence of primary pediatric hypertension and its tracking into adult hypertension point to the importance of determining its pathogenesis to gain insights into its current and emerging management. Considering that the intricate control of BP is governed by a myriad of anatomical, molecular biological, biochemical, and physiological systems, multiple genes are likely to influence an individual's BP and susceptibility to develop hypertension. The long-term regulation of BP rests on renal and non-renal mechanisms. One renal mechanism relates to sodium transport. The impaired renal sodium handling in primary hypertension and salt sensitivity may be caused by aberrant counter-regulatory natriuretic and anti-natriuretic pathways. The sympathetic nervous and renin-angiotensin-aldosterone systems are examples of antinatriuretic pathways. An important counter-regulatory natriuretic pathway is afforded by the renal autocrine/paracrine dopamine system, aberrations of which are involved in the pathogenesis of hypertension, including that associated with obesity. We present updates on the complex interactions of these two systems with dietary salt intake in relation to obesity, insulin resistance, inflammation, and oxidative stress. We review how insults during pregnancy such as maternal and paternal malnutrition, glucocorticoid exposure, infection, placental insufficiency, and treatments during the neonatal period have long-lasting effects in the regulation of renal function and BP. Moreover, these effects have sex differences. There is a need for early diagnosis, frequent monitoring, and timely management due to increasing evidence of premature target organ damage. Large controlled studies are needed to evaluate the long-term consequences of the treatment of elevated BP during childhood, especially to establish the validity of the current definition and treatment of pediatric hypertension.

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Pediatric hypertension; Renal dopaminergic system; Salt sensitivity; Fetal programming; Pharmacogenetics; Renin-angiotensin-aldosterone system

Introduction

According to the National Health and Nutrition Examination Survey from 2011 to 2014, 29% of adults have hypertension, with non-Hispanic blacks having the highest prevalence of 41.2% [1]. Twenty-five years ago, the prevalence of pediatric hypertension in the USA was approximately 0.3–1.2%. Current epidemiological data suggest that at least 1 in 10 children is prehypertensive, while 4 in 100 children are hypertensive [2]. This substantial upsurge is attributed to the obesity epidemic and high salt intake, risk factors similar to those for adult primary hypertension [2–5, 6•]. According to the World Health Organization, adult hypertension is the leading risk factor for morbidity in middle-income countries and second only to tobacco smoking in low and high-income countries. The blood pressure (BP) trends in children may not be related to the country's economic status, although data are not available for low-income countries [4]. In the USA, the prevalence of hypertension in obese children is 11% in 2013 [5]. Comparable prevalence of pediatric hypertension and its risk factors are also seen in Asia [6•]. There has been a 0.19% increase per year in the prevalence of hypertension, adjusted for height, among Chinese children in the past 20 years [7]. The increasing prevalence of hypertension in children may not be related solely to increasing obesity [2–5, 6•, 7].

Elevated BP during childhood is a risk factor for adult hypertension, bearing in mind that not all children with elevated BP have elevated BP as adults and that many adults with hypertension have normal BP during childhood [4]. Indeed, the predictive value of childhood hypertension for adult hypertension has been estimated to vary from 19 to 65% [5, 8]. Nevertheless, there is some predictability of adult BP from childhood values and juvenile target organ damage, which includes left ventricular hypertrophy, carotid intima-media thickening, and decreased neurocognitive performance and brachial flow-mediated dilation [9, 10, 11•]. Higher systolic BP in male children and adolescents with a family history of hypertension increases the risk of developing long-term arterial stiffness, determined by brachial-ankle pulse wave velocity [11•].

Pediatric Hypertension

The consensus-based guidelines of the National High Blood Pressure Education Program and National Heart, Lung, and Blood Institute define pediatric hypertension on the basis of percentiles according to age, height, and sex [12]. Hypertension is defined as systolic blood pressure (SBP) or diastolic BP (DBP) at or above the 95th percentile. Prehypertension is defined as SBP or DBP from 90th to <95th percentile. Stage 1 hypertension is defined as SBP or DBP from 95th to 99th percentile plus 5 mmHg and stage 2 as SBP or DBP >99th percentile, plus 5 mmHg. Normal BP is defined as SBP and DBP that are <90th percentile for sex, age, and height. The accepted BP is the average of three readings of SBP or DBP in a controlled environment after 5 min of rest, with the patient seated and the right arm

supported at heart level. The 2016 European Society of Hypertension (ESH) similarly defines hypertension according to the 2004 US Task Force. The 2016 ESH recommends that normotensive children should be reevaluated every 2 years and those with high-normal BP and no organ damage should be reevaluated after 1 year. However, hypertension in older adolescents is defined by the 2016 ESH as BP at the 95th percentile or greater for age, sex, and height. Moreover, patients 16 years or older with hypertension should be graded as for adults.

In addition to normal BP and “usual” hypertension, there are other subclasses of hypertension including: (i) white-coat hypertension, (ii) masked hypertension, (iii) isolated systolic hypertension, (iv) central hypertension, and (v) exercise hypertension. Based on the effect of NaCl intake on BP, the classes of BP are: (i) salt-resistant BP, which includes (a) salt-resistant normotensive and (b) salt-resistant hypertensive, and (ii) salt-sensitive BP, which includes (a) salt-sensitive normotensive and (b) salt-sensitive hypertensive. There is another subclass called inverse salt-sensitive where the BP is increased by a very low salt diet (vide infra).

BP should be measured by the auscultatory method, using the arm with a properly calibrated and validated instrument, usually a mercury sphygmomanometer [13]. If hypertension is detected by an oscillometric method, it must be confirmed by the auscultatory method. Chronic ambulatory BP monitoring is being supported because it can differentiate sustained hypertension from white-coat, masked, non-dipping (decrease in BP <10% while sleeping), and overly dipping hypertension (decrease in BP >20% while sleeping) [14].

The risk for primary hypertension in children is increased several factors, including low birth weight, male sex, African-American ethnicity, sedentary lifestyle, family history of hypertension, and especially by elevated body mass index [2–5, 13]. By contrast, secondary hypertension is linked to non-obese younger children, lower glomerular filtration rate, and higher DBP [15]. Sixty to 90 % of secondary hypertension is accounted for by renal parenchymal, renovascular, and endocrine etiologies [16].

Pathogenesis of Primary Pediatric Hypertension

Fetal Programming

Fetal programming is the association of adverse events in pregnancy with long-lasting effects into adulthood. This concept was introduced by Barker et al. in 1989 when they noted an inverse relationship between birth weight and SBP [17••]. They hypothesized the “thrifty” phenotype where malnutrition of the mother leads to fetal and infant malnutrition, and ultimately to changes in growth, metabolism, and vasculature in the offspring. All of these effects culminate into the metabolic syndrome, which is characterized by hypertension, obesity, dyslipidemia, and insulin resistance. In the Avon Longitudinal study of Parents and Children, Fraser et al. noted that the offspring of hypertensive mothers had elevated BP by 17 years of age; however, there were no differences in insulin, glucose, or lipid values from the normotensive group [18•].

The prenatal manipulations that have been used to study the effect of prenatal environment on the offspring include the following: (i) maternal and paternal nutrition, including the intake of alcohol; (ii) nicotine exposure; (iii) maternal glucocorticoids; (iv) maternal infection; and (v) placental dysfunction [19]. The elevation of BP of the offspring of pregnant mothers with these prenatal manipulations is caused by several mechanisms, including genetics, epigenetics, inflammation, endoplasmic reticulum stress, and oxidative stress [19–22].

Prenatal insults constrain capillary density, endothelial function, and the development of the kidney, which result in adult hypertension [21, 22]. In humans, nephrogenesis continues until 34 to 36 weeks of gestation, after which no new nephrons are formed. Reduced nephron number contributes to fetal programming of adult hypertension [22]. This agrees with Brenner's hyperfiltration hypothesis which states that the compensatory mechanism of the remaining nephrons results in hastened decline of renal function [23•]. Kidney volume has been used as a surrogate indicator for nephron number. However, kidney volume is positively, rather than negatively, correlated with SBP in children 4–20 years of age [24•]. Furthermore, decreased capillary sprouting increases vascular resistance, leading to increased BP. Preterm infants with excessive exposure to atmospheric oxygen produce free radicals which injure vasculogenesis [25•].

There are sex differences in the fetal programming of hypertension. Experimental models show differences in the effects of developmental insults on males and females through a hormonal milieu (Table 1). Testosterone appears to have a permissive effect, while estrogen has a protective effect, on hypertension in the adult offspring with intrauterine growth retardation (IUGR) [23•, 26••]. Increasing age also leads to sex-specific susceptibility of impaired BP regulation through an age-dependent increase in adiposity, leading to increased plasma leptin that activates the renal sympathetic nerves [23•, 27].

Maternal and Paternal Nutrition—Maternal nutrition plays a role in developmentally programmed hypertension [28, 29]. A high-salt diet during gestation and lactation in Sprague-Daley rats results in increased BP in adult male offspring [30]. Female offspring have lesser increase in BP and even a decrease in BP in some studies [31]. High-salt diet limited to the gestational period or only during weaning [32] may not be associated with hypertension in male or female adult offspring [33]. However, high-salt diet 30 days after birth (dams fed high-salt diet before weaning) increased the BP of adult male offspring [34]. The increase in BP has been related to increased pressor response related to calcium and PKC signaling [35]. Twelve-week-old offspring of Sprague-Dawley dams fed high-salt diet had normal BP but had increased wall thickness of central (aorta, carotid), muscular (mesenteric) and intrapulmonary arteries, regardless of the post-weaning diet [36]. Some offspring of high-salt diet-fed dams had low BP and heart rate, indicative of both left ventricular systolic and diastolic function, and decreased aortic vasodilatory response to nitric oxide [32]. Both high and low maternal salt intakes during pregnancy have been reported to decrease nephron number and increase BP in male offspring [37].

A high fructose diet in pregnant Sprague-Dawley rats also increases BP and aggravates the increase in BP caused by a high-salt diet in male offspring [38]. The mechanisms involved

may include the arachidonic acid pathway and the renin-angiotensin system [30]. The increase in BP in the off-spring of dams fed a high-sucrose diet related to increased reactivity to angiotensin II involves calcium signaling, akin to those observed in offspring of pregnant mothers fed a high-salt diet [39•].

High-fat diet in rat dams during pregnancy increases both SBP and DBP; high-fat diet during lactation increases the DBP and other features of the metabolic syndrome in female but not male offspring [40]. A paternal high-fat diet before conception and after birth also leads to hypertension with features of the metabolic syndrome in the offspring [41•]. Statins given to mouse dams during the second half of pregnancy and lactation decreases metabolic risk in both mother and female offspring [42]. The beneficial effect of statins in the female offspring has been related to a decrease in C-reactive protein-induced inflammation [43]. High paternal fat diet may also disturb fetal programming of metabolism through epigenetic changes [41•]. Sirtuins (SIRT1 and SIRT3) are proposed to mediate the fetal programming of obesity, as well as its myriad long-term effects [44•]. Despite the multiple links of maternal obesity to childhood obesity, prenatal weight management did not show any differences in infant growth [45].

High protein diet during pregnancy in Wistar-Kyoto rats does not affect nephron number or BP in adult offspring [46]. However, low protein diet or maternal undernutrition during pregnancy leads to the metabolic syndrome in the offspring [47]. Protein restriction during pregnancy was also associated with decreased nephron number [48] and cardiac dysfunction [49]. In Wistar rats, maternal protein restriction led to increased BP in F1 and F2 but not F3 generation in both adult male and female rats [50•]. F1 but not F2 male offspring of pregnant guinea pigs that had a 30% reduction in food intake during pregnancy also develop hypertension [51]. The high BP in male offspring is glucocorticoid-dependent without modulation of renal angiotensin receptor; however, it is glucocorticoid-independent and associated with decreased renal AT_2R expression in female offspring [52]. The cardiac dysfunction may be restricted to the male rat offspring [53]. Maternal protein restriction leads to sympathetic overactivity and oxidative dysfunction at the medulla oblongata of Wistar rat dams [54]. There is an increase in circulating leptin in the adult offspring [55]; leptin can stimulate the sympathetic nervous system in rodents [56•]. Chronic administration of leptinin humans does not increase BP [56•]. Small-for-gestational-age offspring of mothers fed with low-protein diet have higher mu-opioid receptor and dopamine type 1 receptor binding but not with dopamine transporters in mesolimbic brain regions. Changes in these neurotransmitter pathways may affect the development of obesity, attention-deficit/hyperactivity disorder, and addiction [57]. BP was not measured in these studies although mood disorders and cardio-metabolic diseases have genetic overlap [58]. Impaired renal dopamine production or function can result in hypertension [59, 60•, 61–65]. There is increased sodium transport in the renal medullary thick ascending limb due to increased NKCC2 expression in rat dams fed a low-protein diet [66]. The hypertension may be associated with salt sensitivity [67]. Undernutrition in sheep dams leads to increased expression of several extracellular matrix proteins in the carotid arteries, related in part to suppression of miR-29c that may involve glucocorticoids [68•]. Low-protein diet during pregnancy has been reported to lead to enhanced responsiveness to angiotensin II [69], especially in male off-spring [70], and exaggerated proliferative response to vascular injury

in the offspring with increased expression of genes related to oxidative stress [71]. By contrast, in the hypothalamus, angiotensin II type 1 receptor is decreased in offspring of Wistar rats fed a low-protein diet [72]; the effect of this apparent difference in central and peripheral angiotensin II expression/function on renal function and BP remains to be determined. miRNAs may play a role in increasing susceptibility to the development of cardio-metabolic disease in off-spring of mothers with abnormal nutrition during gestation or lactation [73]. Some of the programmed effects may be reversible, for example, by inhibition of soluble epoxide hydrolase [74••] and use of antioxidants, such as melatonin and N-acetylcysteine in pregnant rats with nitric oxide deficiency [75••] and seed extract of *Euterpe oleracea* [76••].

High multivitamin intake during pregnancy in Wistar rats results in high BP, high fasting glucose and insulin in male offspring [77, 78•]. However, both male and female offspring fed an obesogenic diet led to increased body weight, glucose intolerance, and high BP [79]. This was prevented by continued high multivitamin or folic acid intake [80].

Maternal Glucocorticoids—Excessive exposure to endogenous or exogenous synthetic glucocorticoids during pregnancy is associated with low birth weight and hypertension in animal models [37]. Steroid administration to pregnant sheep and rats [81–83] but not mice are associated with increased BP in adult offspring [84••] that is sex-specific. Betamethasone administered to pregnant ewes caused hypertension in the 0.5-month-old male offspring that has been related to decreased expression of angiotensin 1–7 Mas receptor in the dorsal medulla and increased angiotensin-converting enzyme in the cerebrospinal fluid [85, 86]. Steroids given to pregnant mice cause dysregulation of the RAAS in 6- and 12-month-old male but not female offspring [87]. Short-term administration of corticosteroids to pregnant mice decreases nephron number in female and male offspring [87]. At 6 months of age, male but not female offspring had increased plasma aldosterone, renal expression of angiotensin II, and Na^+,K^+/ATPase alpha1 subunit and sodium ion channels; blood measure was not measured [87]. However, at 12 months of age, the male but not female mice had decreased BP [88]. Other studies have reported an increase in BP in 6–7-month-old female offspring [83]. The increased BP of male offspring of pregnant rats given dexamethasone has also been related to increased levels of asymmetric dimethylarginine (an endogenous inhibitor of nitric oxide synthase) and increased expression of renal NCC and NHE3, effects that were prevented by administration to the mother rat of L-citrulline, which can be converted to arginine, a substrate of nitric oxide synthase [89]. Placental 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) inactivates the conversion of cortisol to cortisone in humans; thus, a deficiency or dysfunction of the enzyme (e.g., in cases of zinc deficiency) causes excessive fetal exposure to cortisol [90]. Preeclampsia, preterm labor, IUGR, and treatment with dexamethasone or betamethasone to hasten lung maturity all compound the increased exposure to corticosteroids. Long-term consequences are numerous, which include increased the risk for allergies, infection that may be related to decreased immunity, insulin resistance, type I diabetes mellitus, and reduction in nephron number [91], in addition to hypertension [92, 93]. However, maternal glucocorticoids may not directly cause the hypertension in the offspring [94]. It has been suggested that the inconsistency in the increase in BP after prenatal exposure to glucocorticoids in rodents could indicate that hypertension becomes

apparent only under stressed conditions and that the use of tail cuff to measure BP contributed to the irregularity [95]. The absence of glucocorticoid-inducible kinase SGK1 in the mother prevents the ability of prenatal protein restriction to increase the BP in adult male and female offspring.

Maternal Infection—There is a positive relationship between infection during pregnancy and adverse outcomes in the off-spring, including cardiovascular diseases [96•, 97•]. Maternal bacterial infection has been mimicked by the systemic administration of the gram-negative bacterial endotoxin lipopolysaccharide (LPS) to dams. Exposure of rat dams to LPS results in increased BP in the offspring that is related to oxidative stress and inflammation [96•, 97•, 98, 99]. The increased BP was found in both male and female offspring [100]. The increase in BP caused by prenatal exposure to LPS has been suggested to be the result of increased sympathetic nerve activity, increased activity of the RAAS, impaired endothelium-dependent and endothelium-independent vascular relaxation, and decreased activity of the renal dopaminergic system [96•, 97•, 98]. The impaired vascular relaxation is caused by decreased vascular expression of connexin 37, endothelial nitric oxide synthase, NO production, and soluble guanylyl cyclase [96•]. As will be discussed below, the renal dopaminergic system is important in the regulation of BP by enabling the kidney to excrete a sodium load during conditions of normal or moderate increase (5–10% acute saline load, or about 200–250 mmol sodium intake/day) in sodium intake. The increase in reactive oxygen species (ROS) in the offspring of dams that received LPS also increased the renal expression and activity of G protein-coupled receptor kinase type 2 (GRK2) and type 4 (GRK4). These kinases are upstream of dopamine receptors (D_1R and D_3R) and angiotensin type 1 receptor (AT_1R). Variants of human GRK4 impair D_1R and D_3R function but increase AT_1R expression and function [101••] which ultimately lead to hypertension in humans and transgenic mice expressing human GRK4γ142V. The impairment of renal dopamine receptor function also impairs the ability of the kidney to excrete an oral sodium load (gastro-renal communication) [102•]. There may be differences in organ response to maternal LPS administration because D_2R not D_1R expression is decreased in the prefrontral cortex of Sprague-Dawley rat offspring [103]. These apparent discrepancies need to be sorted out because the administration of a proinflammatory cytokine inductor, polyriboinosinic polyribocytidilic acid (poly[I:C]), during gestational day 14–16 in Sprague-Dawley rats increased baseline extracellular dopamine levels in the nucleus accumbens, but not in the prefrontal cortex of their offspring; their ventral tegmental neurons had reduced activity but normal D_2R autoreceptor activity [104].

Interestingly, although prenatal exposure to LPS or high-fat diet increased the BP of the offspring, the combination of prenatal exposure to LPS and pre- and post-natal high-fat diet was associated with normalization of BP [98]. This discordant result has been suggested to be the result of adaptive response to inflammation because a high-fat diet can increase plasma LPS levels [98, 105].

Placental Dysfunction—Utero-placental insufficiency is a leading cause of IUGR and low birth weight even with normal maternal nutrition. There are several models of utero-placental insufficiency, including ligation of either the ovarian or uterine arteries [106]. F1

and F2 male but not female offspring of Wistar-Kyoto rat dams with uteroplacental insufficiency caused by bilateral uterine vessel ligation developed hypertension at 6 months of age that could be related, in part, to impaired vasorelaxation and arterial stiffness, especially in the mesenteric artery [107, 108]. Female offspring which were not hypertensive had normal mesenteric, renal, and femoral artery stiffness but had uterine artery endothelial dysfunction and increased wall stiffness [109••]. Utero-placental insufficiency has been shown to decrease nephron number and cyclooxygenase-2 (COX-2) in a rat model [110] and to increase umbilical and carotid artery stiffness in sheep dams due to disrupted extracellular matrix deposition [111]. Increased markers of renal apoptosis and decreased urinary sodium excretion [112] were also noted in rats and newborn piglets. There are sex differences in the development of hypertension in the IUGR offspring; 12-week-old male rats with IUGR have elevated mean arterial BP compared to females [106]. Furthermore, adult IUGR female rats have higher vascular endothelial growth factor (VEGF) levels than IUGR males but have similar lower VEGF levels at birth [113]. Testosterone has a modulating role in the hypertension of adult male offspring of rat dams with placental insufficiency [114•].

Genetics and Pharmacogenetics of Primary Hypertension: Role of GRK4

Hypertension, a complex trait caused by interactions of genetic, epigenetic, environmental, and behavioral factors, is a major public health problem because of its high prevalence and increased risk for cardiovascular and renal diseases [115]. Considering that the intricate control of BP is governed by a gamut of anatomical, molecular biological, biochemical, and physiological systems, multiple genes are likely to influence an individual's BP and susceptibility to develop hypertension. The long-term regulation of BP rests on renal and non-renal mechanisms [116••]. One renal mechanism relates to sodium transport. The impaired renal sodium handling in primary hypertension and salt sensitivity could be caused by aberrant counter-regulatory natriuretic and anti-natriuretic pathways. The sympathetic nervous and RAAS are examples of antinatriuretic pathways. An important counter-regulatory natriuretic pathway is afforded by the renal autocrine/paracrine dopamine system, aberrations of which are involved in the pathogenesis of hypertension [116••], including that associated with obesity. As indicated earlier, LPS administration to rat dams induces the hypertensive phenotype in the offspring that is related to an increase in the renal expression and activity of GRK2 and GRK4 [97•]. Because GRK4 fulfills all the criteria needed to implicate a gene as a cause of a complex trait, hypertension, in this instance, only GRK4 will be included in this review. The *GRK4* gene is one of the few genes that fulfill the criteria for ascribing a gene as causal of a complex disorder. These criteria include gene linkage and gene variant association, in vitro phenotype, with the definitive evidence involving the expression of the variant genes in transgenic animals [64, 117]. Only the variants of genes of *AGT* that encodes angiotensinogen [118], *AGTR1* that encodes the angiotensin II (Ang II) type 1 receptor (AT_1R) [119], *CYP11B2* that encodes aldosterone synthase [120], and *GRK4* have been shown to cause hypertension in transgenic mice [121, 122]. Variants of ATP2B1, STK39 [123], GRK4, and SLC4A5 [124, 125] have been associated with salt sensitivity; GRK4γ486V causes salt-sensitive hypertension in transgenic mice [126].

Genome-wide association studies (GWAS), which have identified only ≈2–5% of the genetic factors believed to influence BP, failed to associate the *GRK4* variants with hypertension [127–129]. There are several reasons for this non-association, including stringent correction and requirement for independent replication, resulting in higher type 2 error rates and the absence of specific *GRK4* gene variants in the Affymetrix and Illumina chips (vide infra). Nevertheless, using gene-targeted studies, the association of *GRK4* variants with hypertension has been replicated in several ethnic groups [59], with some exceptions [130, 131]. Additional reasons for non-association in GWAS include failure to include epistasis, epigenetics, environment, behavioral influences, e.g., sodium and potassium intake, and age in the analyses. Nutrition and gut microbiota can influence epigenetics [132]. Increased dietary salt can increase oxidative stress [133] and oxidative stress can influence epigenetics (e.g., histone deacetylase 1 activity) [134]. Felder et al. reported that miR-124 expression is increased in urinary exosomes of salt-sensitive subjects [135•] and can regulate c-Myc [136]. C-Myc can regulate GRK4 [135•], probably by interacting with the *GRK4* promoter. This is of interest because of the following reasons: (1) c-Myc is proto-oncogenic [137]; (2) c-Myc is positively associated with hypertension and cancer, at least in males [138]; and (3) increased dietary salt intake increases the risk of gastric cancer [139]. Furthermore, epigenetics can influence gene transcription. Variants in the promoter region of *GRK4* can influence its expression [140], and the salt sensitivity of C57BL/6J mice is related to increased renal expression of GRK4 [141]. Aortic and renal expression of GRK4 is also increased in spontaneously hypertensive rats [142, 143] whose high BP can be increased further by high-salt diet [144].

$GRK4^{142V}$ is not included in the Affymetrix and Illumina chips, except for Illumina Human 1M bead chip [101••]. The only Affymetrix chip that has $GRK4^{486V}$ is Genomewide 6. The Illumina chips, except for Illumina Human 1M-Duov3, do not have $GRK4^{486V}$. Not all the chips have $GRK4^{65L}$ either. It should also be noted that in all the GWAS studies, circulating DNAwas used which may not reflect spontaneous somatic mutations in the kidney that can also cause hypertension. We have reported the association of hypertension and certain DNA and miRNA in urine exosomes and urine renal proximal tubule cells [135•, 145].

GRK4 is upstream of genes that regulate renal function and BP, i.e., those of the RAAS and renal dopaminergic system. *GRK4* variants impair D_1R and D_3R function and increase AT_1R function [116••, 121]. As stated above, this could be related to the ability of *GRK4* variants, via histone deacetylase 1, to positively regulate renal AT_1R expression [121]. The effect of renal dopamine on BP is different from that administered systemically [116••]. The normal circulating concentrations of dopamine (picomolar range) are not sufficiently high to activate endogenous dopamine receptors but high nanomolar to low micromolar concentrations can be attained in dopamine-producing tissues [116••]. The GRK family is normally important in maintaining the responsiveness of certain dopamine receptor subtypes, e.g., D_1R and D_3R. GRK decreases GPCR responsiveness after continued stimulation by agonists through phosphorylation of the receptors and uncoupling them from their G protein complexes [122]. Growing evidence support the association between the allelic variants of *GRK4*, salt sensitivity, hypertension, and response to antihypertensive drugs [101••]. This has been reviewed by Rayner and Ramesar and Yang et al. [64,146]. A recent metaanalysis showed that *GRK4* and *DRD1* gene polymorphisms, rs1024323 *GRK4*

(OR = 1.826) and rs4532 of *DRD1* genes (OR = 1.833), are associated with hypertension in Caucasians and East Asians, respectively [59]. *GRK4* polymorphisms are not associated with preeclampsia in northern Han Chinese [147]. However, *DRD1* (−48G) and *DRD4* (−521T) receptors are associated with preeclampsia in a Polish population [148]. Mice harboring *GRK4* gene variants such as $GRK4\gamma^{486V}$ are hypertensive on a high-salt diet, while mice harboring $GRK4\gamma^{142V}$ variants are hypertensive on a normal salt diet but not affected by a high-salt diet [149••]. These variants with increased constitutive GRK4 activity have been shown to down-regulate the renal dopaminergic system and upregulate RAAS (AT_1R) by decreasing and increasing their expression and activities, respectively, in humans [146]. Furthermore, these variants offer new pharmacogenomic approaches in the treatment of hypertension as evidenced by the African-American Study of Kidney Disease (AASK) where $GRK4^{65L}$ and $GRK4^{142V}$ predict a reduced response to α-adrenergic blockers [149••]. By contrast, $GRK4^{142V}$, by itself, is associated with a more rapid response to a β-adrenergic blockade. In another study in two cohorts with primary hypertension without renal disease, as the number of individual *GRK4* single nucleotide polymorphisms (SNPs; 65R>L and 142A>V) increase, BP response to a β-adrenergic blockade in a mixed population of black and white individuals decreases [150••]. $GRK4^{R65}$ or $GRK4^{A142}$ predicts a good BP response to a decrease in salt intake, whereas $GRK4^{65L}$ or $GRK4^{142V}$ predicts a limited response to reduced salt intake [64]. However, the presence of at least three *GRK4* allele variants (65L, 142V, and 486V), relative to those with fewer than three is associated with a better response to diuretic therapy [151]. The expression of $GRK4^{486V}$, but not $GRK4^{142V}$, in transgenic mice confers salt sensitivity [152] and predicts a response to diuretics in humans with primary hypertension [153]. Among Japanese, $GRK4^{142V}$ predicts a good response to angiotensin receptor blockers [101••].

Target Organ Damage

Systemic target organ damage (TOD) has been clearly documented with elevated BP in children. However, the lowest level of BP that causes TOD has not been determined. One of the earliest changes seen is left ventricular hypertrophy (LVH) without any correlation to severity of BP [154]. Although hypertension is one of the top causes of chronic kidney disease in adults, this is not the case with children. Hypertensive nephrosclerosis, microalbuminuria, and reduced glomerular filtration rates have been reported in children with hypertension [155]. Hypertensive children have been found to have inferior neurocognitive performance, executive function, and decreased cerebrovascular reactivity (CVR) [156•]. Atherosclerotic changes such as increased carotid intimal-medial thickness (cIMT), arteriolar narrowing, and stiffness have also been associated with pediatric hypertension [157]. These pathologic alterations support Folkow's hypothesis that elevated BP thickens the medial layer of the vessels which be-gets hypertension [158•]. Furthermore, these linked with BP tracking in children in which BP during childhood predicts adult blood BP [4, 8–10, 11•]. Therefore, there is a need for early monitoring and treatment of pediatric hypertension such as ambulatory BP monitoring and pharmacologic and non-pharmacologic management of elevated BP [159]. Figure 1 summarizes the pathogenesis of pediatric hypertension showing the causes and effects at different stages of human life.

Conclusions

Despite the increasing prevalence of hypertensive and prehypertensive children in different parts of the world, pediatric hypertension remains an underdiagnosed condition. Reformed normative data on BP inclusive of ethnicity and not just of age, sex, and height are imperative to define pediatric hypertension across all ethnic backgrounds, especially among African-American and Hispanics. The rise of the obesity epidemic in children shifts the onset of metabolic syndrome to an earlier age. Thus, public health measures to reduce this burden are needed as experimental evidence has documented the interaction of hyperglycemia, hyperinsulinemia, renal dopaminergic system dysfunction, upregulation of the RAAS, and hypertension. Larger controlled studies must be done to evaluate the long-term effect of childhood obesity and dietary salt with adult cardiovascular morbidity and mortality. Studies evaluating the effect of interventions on complicated pregnancies and their offspring must also be reassessed because of the evident theory of fetal programming of hypertension.

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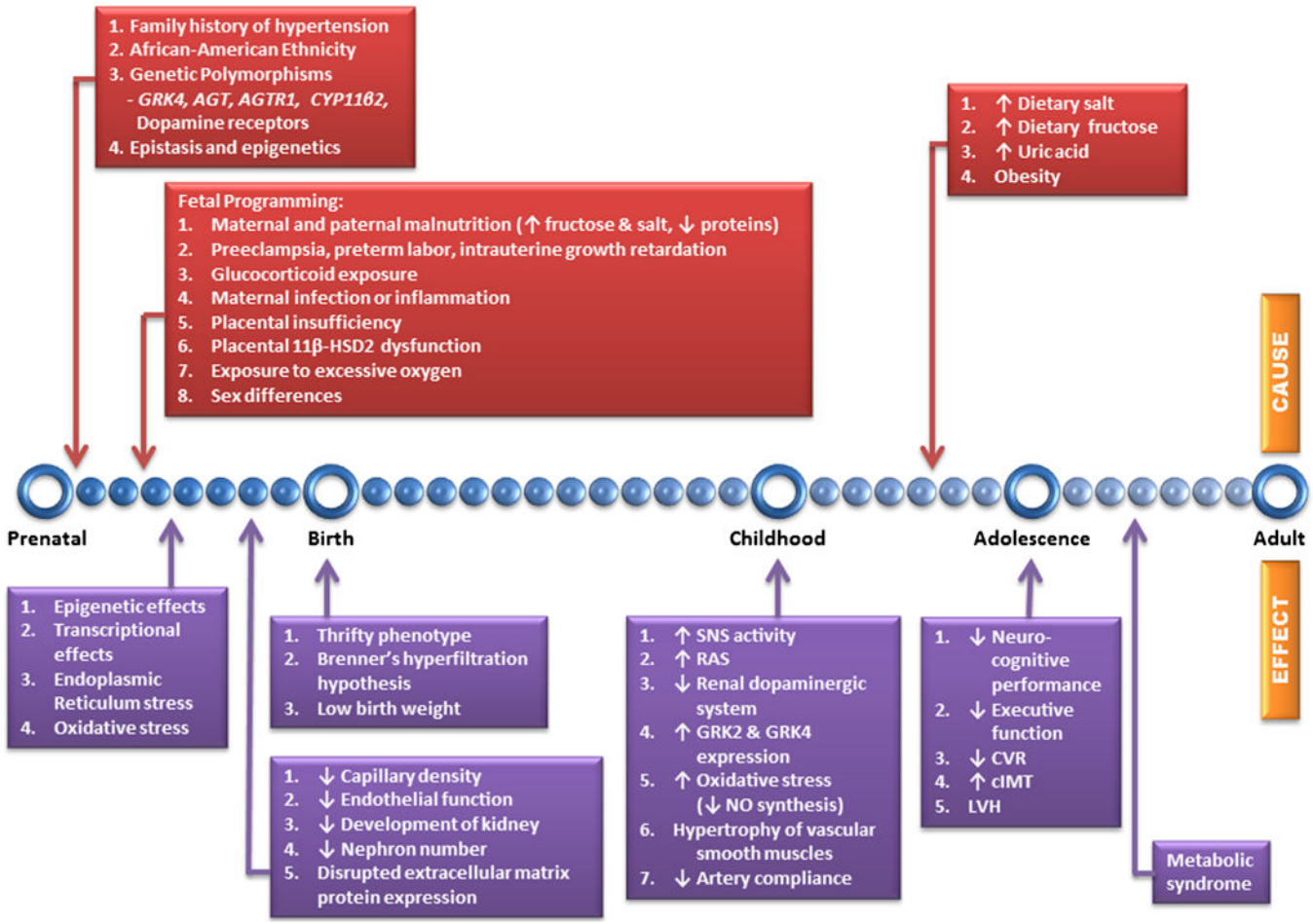

Fig. 1.

Timeline showing the pathogenesis of pediatric hypertension. Identified underlying causes and short-term and long-term effects are shown *above and below the blue line*, respectively. Genetic predisposition, early developmental insults, and dietary influences lead to changes in the regulation of BP that are carried into adulthood. *GRK4* G protein-coupled receptor kinase type 4, *GRK2* G protein-coupled receptor kinase type 2, *AGT* angiotensinogen gene, *AGTR1* angiotensin II (Ang II) type 1 receptor gene, *CYP11β2* aldosterone synthase gene, ↑ increase, ↓ decrease, *11β-HSD2* placental 11β-hydroxysteroid dehydrogenase 2, *SNS* sympathetic nervous system, *RAS* Renin-angiotensin system, *NO* nitric oxide, *CVR* cerebrovascular reactivity, *cIMT* carotid intimal-medial thickness, *LVH* left ventricular hypertrophy

Table 1

Sex differences in the effects of fetal developmental insults through a hormonal milieu

	Male	Female
Hormonal milieu	Testosterone	Estrogen
RAAS	↓[a]	(−)[a]
Nephron number	↓[a]	↓/(−)[a]
Endothelin production	↑[a]	(−)[a]
Reactive oxygen species	↑[a]	↓[a]

[a]↓ = decreased, ↑ = increased, (−) = no change